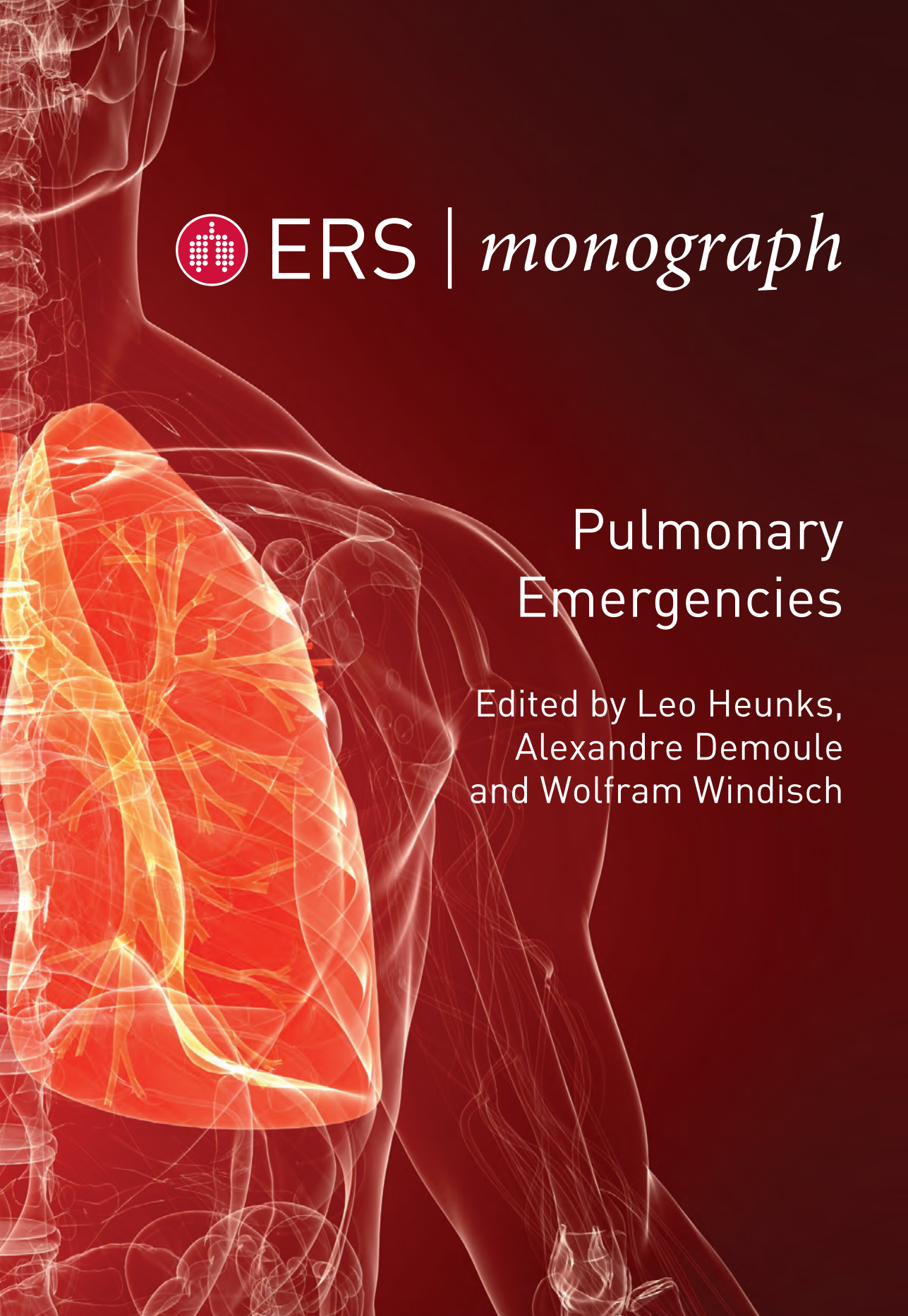

ERS | *monograph*

Pulmonary Emergencies

Edited by Leo Heunks, Alexandre Demoule and Wolfram Windisch

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Leo Heunks, Alexandre Demoule
and Wolfram Windisch

Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Robert Bals

Emergency situations in pulmonary medicine are critical for the patient and often stressful for the care providers. The most important factor in the successful management of such situations is to be prepared. Interruption of the function of the lung immediately results in an emergency situation. In the case of severe impairment of gas exchange, a catastrophic outcome will occur within a few minutes if adequate measures are not started. The management of respiratory acute situations is a core capability of respiratory and emergency medicine. Physicians in all areas of pulmonary medicine face critical situations daily. Maintaining the ability to manage emergencies adequately requires keeping knowledge up to date and training in critical procedures. In addition to the basic principles in this area, a number of new techniques and procedures have been developed in recent years. In contrast to the importance of this subject, there are only a few comprehensive textbooks available.

This *ERS Monograph* aims to provide the reader with a detailed overview of emergencies in pulmonary care, from a viewpoint close to the bedside. The book is split into two sections. The first section, on clinical entities, covers the most important emergency situations, while the second section, on acute pulmonary interventions, focuses on key techniques. This structure allows readers to learn systematically or to refresh their knowledge of the theory of pulmonary emergency management, including bedside interventions. Together with practical training and structural developments, this *ERS Monograph* will enable physicians and other healthcare providers to treat their patients safely in critical situations.

I would like to thank the Guest Editors, Leo Heunks, Alexandre Demoule and Wolfram Windisch, who have worked very successfully to select these topics and integrate them into a comprehensive book. I would also like to thank all the authors for their work. I am sure that this excellent *ERS Monograph* will

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be useful in clinical practice for a broad range of respiratory physicians and will help to improve the care of our patients.

Disclosures: R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.

Guest Editors

Leo Heunks

Leo Heunks is professor of intensive care medicine at the VU University Medical Center Amsterdam (Amsterdam, the Netherlands). He received his undergraduate training and MD at the Radboud University (Nijmegen, the Netherlands). From 1996 to 2000, he was a PhD student in respiratory physiology. During the PhD programme he visited the Mayo Clinic (Rochester, MN, USA) for 7 months to study skeletal muscle single fibre mechanics and intracellular calcium imaging (with mentor Gary Sieck). He trained as a pulmonologist at the Radboud University Medical Center from 2000 to 2006, followed by a 2-year fellowship in intensive care medicine, and became consultant in intensive care at the same hospital. He was co-founder of the first specialised ventilator-weaning unit in the Netherlands and chair of the Dutch guideline for difficult weaning. In 2016, he moved to the VU University Medical Center Amsterdam, Dept of Intensive Care.

His research interests include effects of critical illness on respiratory muscle function, mechanical ventilation, weaning from the ventilator and ARDS. He has spent research fellowships at Loyola University Medical Center (Chicago, IL, USA) and St Michael's Hospital, Toronto (ON, Canada). In both clinical work and research, he promotes the understanding of physiological principles. Only when we are willing to understand the underlying physiology can we conduct meaningful research and optimal patient care.

Currently, Leo Heunks is secretary of European Respiratory Society assembly 2 (respiratory intensive care).

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Alexandre Demoule

Alexandre Demoule is professor of intensive care medicine at the Pierre and Marie Curie University Medical Centre in Paris (France). He is the director of the medical ICU, the step-down unit and the weaning centre within the Dept of Pneumology and Intensive Care Medicine, La Pitié-Salpêtrière hospital in Paris. He was trained in pneumology and physiology at the Pierre and Marie Curie University under the supervision of Thomas Similowski and in intensive care medicine at Paris-Est University in Créteil, where he was also a research fellow (2001–2002) in mechanical ventilation with Laurent Brochard. From 2003 to 2006, he was a PhD student in respiratory physiology at the Pierre and Marie Curie University. During the PhD programme he spent 1.5 years at the Meakins-Christie Laboratories, McGill University (Montreal, QC, Canada), under the supervision of Basil Petrof.

His main research field is patient–ventilator interactions. It involves specific research topics such as brain–ventilator interactions, the impact of mechanical ventilation on respiratory sensations and comfort, and respiratory muscle dysfunction in mechanically ventilated patients. He also conducts clinical studies on noninvasive mechanical ventilation in acute respiratory failure and on new modes of mechanical ventilation. His research projects are conducted within UMR_S 1158, a joint research unit between Pierre and Marie Curie University and the French National Institute of Health and Medical Research (Inserm).

Alexandre Demoule is the chair of the annual meeting of the French Intensive Care Society. He has organised several conferences on mechanical ventilation, is co-author of guidelines in the field of intensive care medicine and serves as an invited speaker at international conferences.

Wolfram Windisch

Wolfram Windisch is the medical director of the Dept of Pneumology and Critical Care Medicine, Clinic of Cologne (Cologne, Germany), and holds the professorial chair for Pneumology at the University of Witten/Herdecke (Cologne). His department is specifically dedicated to the acute and chronic treatment of respiratory failure, invasive and noninvasive mechanical ventilation, extracorporeal lung assist, weaning from mechanical ventilation and sleep medicine. In addition, his other main focuses are COPD/asthma, thoracic oncology, interstitial lung diseases, infectious diseases and cystic fibrosis. His research interests include respiratory physiology, all aspects of mechanical ventilation, monitoring of respiratory function in the acute and

chronic setting, and health-related quality of life in patients with severe chronic respiratory failure.

In addition, Wolfram Windisch has chaired the German Interdisciplinary Society of Home Mechanical Ventilation, the group for noninvasive ventilatory support within assembly 2 of the European Respiratory Society, and the section for intensive care medicine of the German Society of Pneumology and Ventilation. He has organised several symposia and conferences on mechanical ventilation and serves as an invited speaker at national and international conferences. He also serves as the responsible author for the German guidelines for noninvasive and invasive mechanical ventilation for treatment of chronic respiratory failure, and has served as a co-author for the German guidelines on acute NIV and for the German guidelines on prolonged weaning.

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Introduction

Leo Heunks[1], Alexandre Demoule[2,3] and Wolfram Windisch[4]

Pulmonary emergencies are potentially life-threatening conditions that require immediate attention to avoid delay in treatment. These patients most often present with severe dyspnoea, but other symptoms and signs may include collapse, chest pain and haemoptysis. A variety of healthcare professionals, such as pulmonologists, emergency room (ER) physicians, intensivists, general internists, anaesthesiologists, respiratory therapists, residents and ER nurses, may be involved in the acute care of these patients. The differential diagnosis of a pulmonary emergency, *e.g.* presenting with dyspnoea, may be very broad and could result from dysfunction of the airways, lung parenchyma or pulmonary vasculature. In every patient presenting to the ER, this differential diagnosis should be considered.

In this *ERS Monograph*, the most common and also rather less common causes for pulmonary emergencies are described. Each chapter discusses pathophysiology, differential diagnosis and treatment strategies. In addition, the last five chapters describe common pulmonary interventions in detail. The chapters are written by recognised experts in their field and all chapters have been peer reviewed. Thanks to the effort of so many professionals, this has become a very impressive *ERS Monograph* that will definitely be of value to all colleagues involved in the care of patients with pulmonary emergencies.

We would like to thank all the authors, reviewers and ERS staff for their time and effort to make this *ERS Monograph* a success.

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List of abbreviations

ARDS	acute respiratory distress syndrome
BAL	bronchoalveolar lavage
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CT	computed tomography
ECMO	extracorporeal membrane oxygenation
FEV_1	forced expiratory volume in first second
F_{IO_2}	inspiratory oxygen fraction
ICU	intensive care unit
NIV	noninvasive ventilation
P_{aCO_2}	arterial carbon dioxide tension
P_{aO_2}	arterial oxygen tension
PEEP	positive end-expiratory pressure
RCT	randomised controlled trial
S_{pO_2}	arterial oxygen saturation measured by pulse oximetry

Pneumothorax

Steve Walker and Nick Maskell

Pneumothorax is a heterogeneous condition whose presentation and disease course are influenced by individual phenotypes, risk factors and underlying pathophysiology. The management of pneumothoraces should be personalised, taking into account the presenting patient with their symptoms and accompanying chest imaging, as well as their risk of developing a subsequent pneumothorax. Further understanding of risk stratification, newer treatment options such as ambulatory devices and further research into the role of conservative management are likely to influence future management pathways.

Pneumothorax is a relatively common clinical problem. Despite its prevalence, there are many areas of recognised uncertainty in the natural history and management of the condition. This chapter provides an overview of the epidemiology and pathogenesis of pneumothoraces, and how these influence current management strategies, as well as the rationale behind newer individualised treatment strategies and the future treatment of pneumothoraces.

Pneumothorax is defined as air in the pleural space [1] and is classically categorised into spontaneous or traumatic. Spontaneous pneumothoraces occur without preceding trauma and are further categorised into primary or secondary, depending on the absence or presence of underlying lung disease, respectively. Traumatic pneumothoraces arise as a result of direct or indirect trauma to the chest. When these occur as a result of a procedure, they are termed iatrogenic. The focus of this chapter will be spontaneous pneumothoraces.

The American College of Chest Physicians (ACCP) Delphi consensus 2001 [2] and the British Thoracic Society (BTS) guidelines 2010 [3] have guided recent management of pneumothoraces. While there is disparity between the two guidelines, the underlying premise of removing air from the pleural space in a symptomatic or large pneumothorax is the same. A recent task force statement from the European Respiratory Society in 2015 reviewed the current evidence and highlighted areas of uncertainty, particularly how to identify patients at risk of reoccurrence and those suitable for early definitive treatment [4].

Epidemiology

Primary spontaneous pneumothorax (PSP) has an annual incidence of 7.4 per 100 000 population in males and 1.2 per 100 000 in females [5]. The annual incidence of secondary

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spontaneous pneumothorax (SSP) is 6.3 per 100 000 population in males and 2.0 per 100 000 in females [5]. There is bimodal distribution, with a peak incidence in young people aged 15–34 years and another in those aged >55 years [6]. These peaks are often associated with PSP and SSP, respectively [6].

Smoking is the most important risk factor in PSP. The relative risk of a first PSP was increased 22-fold in men who smoked, and ninefold in women, compared with nonsmokers, with a lifetime risk of developing pneumothorax of 12% in smoking males compared with 0.1% in nonsmoking males [7]. There is a strong dose–response relationship between the risk of pneumothorax and the number of cigarettes smoked per day [7].

Cannabis smoking, causing bullous disease, is another risk factor for pneumothorax [8]. Male sex [9], height [9] and a low BMI [10] are also associated with increased risk of PSP. There are also a range of inherited disorders that predispose to pneumothorax, including Marfan syndrome [11] and cystic lung disorders such as Birt–Hogg–Dubé syndrome [12] and pulmonary lymphangioleiomyomatosis (LAM). LAM is a rare disease that characteristically affects women of reproductive age. It causes smooth muscle infiltration and cystic destruction of the lung. It is thought that the prevalence of LAM in nonsmoking women aged between 25 and 54 years with a spontaneous pneumothorax is 5%, with 70% of patients with LAM having a pneumothorax at some point in their disease course [13]. A temporal relationship between pneumothorax and menses has been identified. Catamenial pneumothorax, which can occur 72 h either side of the start of menses, has been shown to be responsible in >30% of pre-menopausal women who were treated surgically for PSP [14].

Pathophysiology

Historically, PSP and SSP have been divided into two separate pathophysiological groups. SSP, a pneumothorax that occurs in patient with known lung disease, occurs across a spectrum of diseases and the pathogenesis is multifactorial. Airways diseases (*e.g.* COPD, asthma, cystic fibrosis) are the most common underlying diseases, although infectious lung disease (*e.g. Pneumocystis jiroveci* infection, tuberculosis, necrotising pneumonia), interstitial lung disease, connective tissue disease and cancer can also be underlying causes [15].

PSP is categorised by the absence of apparent lung disease. It has, however, become clearer that the majority of patients with PSP have evidence of lung abnormalities, such as emphysema-like changes, subpleural blebs and bullae. These emphysema-like changes were identified by CT in a case–control series in 81% of nonsmokers with PSP compared with 0% of healthy volunteers [16].

These lung abnormalities, identified on CT and thoracoscopy, are thought by many to be responsible for pneumothorax and are often the target for surgical management. It has been hypothesised that there is progression from normal pleura to blebs to the larger bullae, which can then rupture [17]. This view, however, is not universal, with many patients not having detectable blebs [18]. Furthermore, studies comparing the appearance of blebs and bullae after the first episode of PSP and those in recurrent PSP by medical thoracoscopy did not find any significant difference in size, number or location of the blebs and bullae, suggesting that they may not be a major risk factor [19]. The concept of pleural porosity is another mechanism that has been proposed in the formation of a pneumothorax, in additional to macroscopic changes. This hypothesis was investigated by

Noppen *et al.* [20] using fluorescein during thoracoscopy to visualise parenchymal abnormalities of the visceral pleural and to determine whether this was localised to blebs. Extensive subpleural fluorescein accumulation and fluorescein leakage, which they described as high-grade lesions, were present exclusively in PSP and were not necessarily associated with blebs or bullae or with other abnormalities visible on white-light inspection. They described this as pleural porosity, postulating that loss of surface mesothelial cells, thinning and rupture of the basement membrane, and/or downregulation of junctional proteins may play a role. The concept of diffuse pleural porosity may explain the reported significantly higher recurrence rates if pleurodesis of some form had been omitted during video-assisted thoracoscopic surgery (VATS) [21].

The hypothesis that air trapping from peripheral airway obstruction could result in a pressure increase, resulting in pneumothorax, was investigated in a study examining lung density values in CT in patients with PSP and in normal volunteers [22]. It showed lower lung densities, suggestive of air trapping, in patients with PSP. This was independent of smoking and bullous disease [22]. The authors concluded that air trapping may be a contributing factor in the pathogenesis of PSP. A study by Bintcliffe *et al.* [23] used CT to investigate the lung structure and extent of emphysema in patients with PSP or SSP and in a control group. They found that the majority of patients with PSP had quantifiable evidence of parenchymal destruction and emphysema. Patients with PSP who smoked had significantly greater low-attenuation areas than patients with PSP who were nonsmokers [23]. The presence of these abnormalities in patients with PSP, combined with the demonstrated relationship with smoking, belies the idea that PSP occurs in normal lungs.

Diagnosis

Patients with PSP often have minimal or absent symptoms. PSP can present with chest pain (81%) and less commonly dyspnoea (39%) [24]. It is not provoked by exercise and typically occurs at rest (80%) [24]. SSP usually presents with dyspnoea and can be accompanied by chest pain, hypoxaemia, hypotension and hypercapnia. The patient may be very unwell with their underlying lung disease.

Characteristic physical findings are ipsilateral diminished breath sounds, reduced lung expansion and hyperresonance.

Diagnosis is confirmed by a posterior–anterior chest radiograph with displacement of the pleural line, with absent lung markings distally (figure 1). An air–fluid level is visible in 50% of cases [25]. There is no benefit in an expiratory film [26].

Thoracic ultrasound is being used more frequently in the diagnosis of pneumothorax, particularly in the emergency trauma and critical care setting. In this setting, it has been shown to be more sensitive and specific than a chest radiograph, with one study demonstrating a sensitivity for ultrasound of 98% and a specificity of 99% [27]. However, there is limited evidence behind its use in spontaneous pneumothorax.

Chest CT is regarded as the "gold standard" [3] in the detection of pneumothorax and can be helpful to further investigate complex pneumothoraces, identify small pneumothoraces and distinguish pneumothorax from bullae in patients with SSP. The latter can be particularly challenging with a plain chest radiograph. A visceral pleural line running

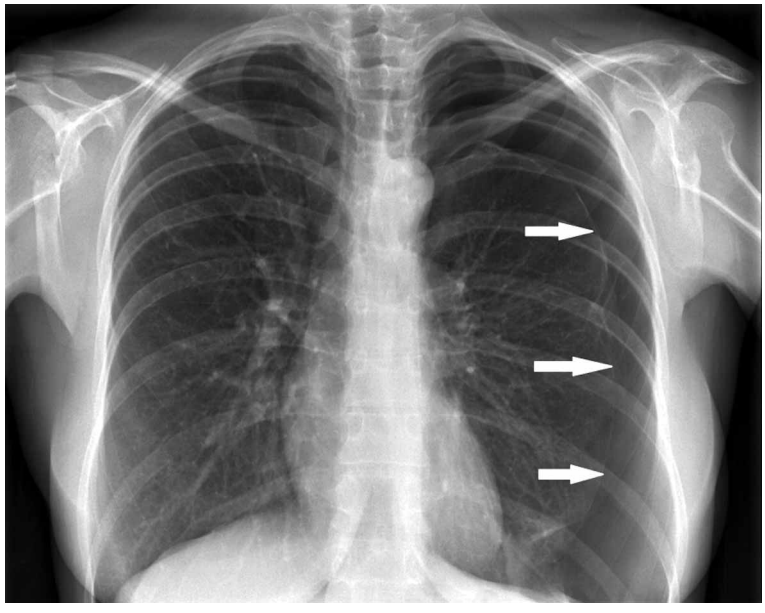

Figure 1. Chest radiograph of a left-sided pneumothorax (indicated by white arrows).

parallel to the chest wall is more suggestive of a pneumothorax, while bullae have a concave appearance (figure 2).

Management

As outlined above, pneumothorax is a heterogeneous condition, influenced by individual modifiable and nonmodifiable risk factors and pathophysiology, and accordingly should be managed in a personalised way. The management of spontaneous pneumothorax can be

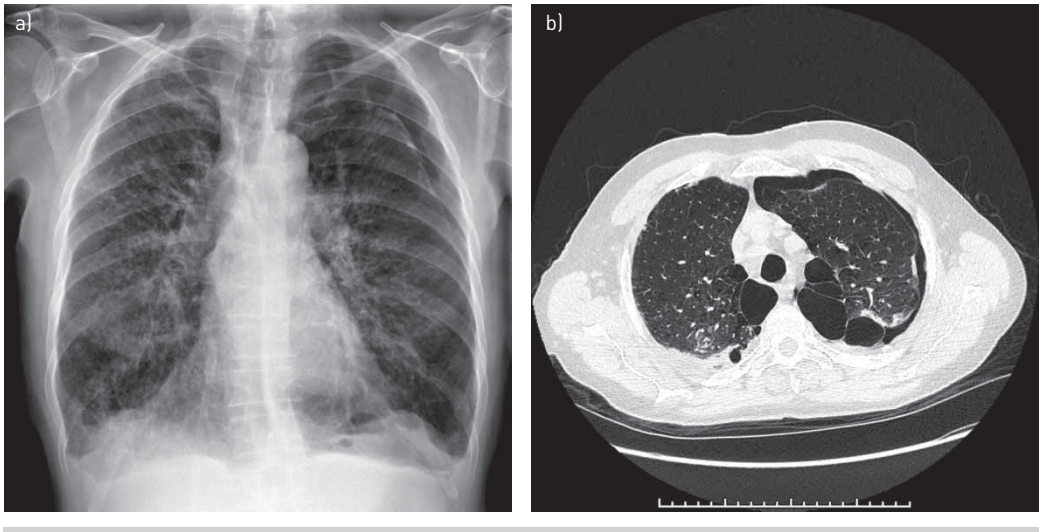

Figure 2. a) Chest radiograph of a left-sided secondary spontaneous pneumothorax and bullous emphysema with b) corresponding chest CT.

divided into three areas: 1) immediate management of the pneumothorax; 2) how and when to deal with failure of initial management; and 3) how to prevent reoccurrence.

Immediate management

The immediate management of spontaneous pneumothorax is determined by several factors. If the patient is haemodynamically unstable or has bilateral pneumothoraces, then a chest drain should be inserted as a first line [3]. If the patient is thought to be in tension, they should be managed as detailed below, with needle decompression and a chest drain (figure 3). For all other pneumothoraces, the management pathway, outlined by the ACCP Delphi consensus 2001 [2] and the BTS guidelines 2010 [3] is determined by: 1) whether the pneumothorax is deemed primary or secondary; 2) the presence of symptoms; and 3) the size of the pneumothorax on chest radiograph.

If a patient has a PSP, is asymptomatic and has a small pneumothorax, then a conservative management plan of monitoring is advocated by the BTS [3]. The rate of resolution of an untreated PSP has been calculated by CT volumetry at 2.2% per day [28]. The use of high-flow oxygen in treatment of pneumothorax was shown to speed up the resolution of PSP fourfold when patients were admitted for observation [29].

If the patient is symptomatic or has a large pneumothorax, an intervention to remove the air from the pleural space is advised. The ACCP and BTS differ on the definition of a large

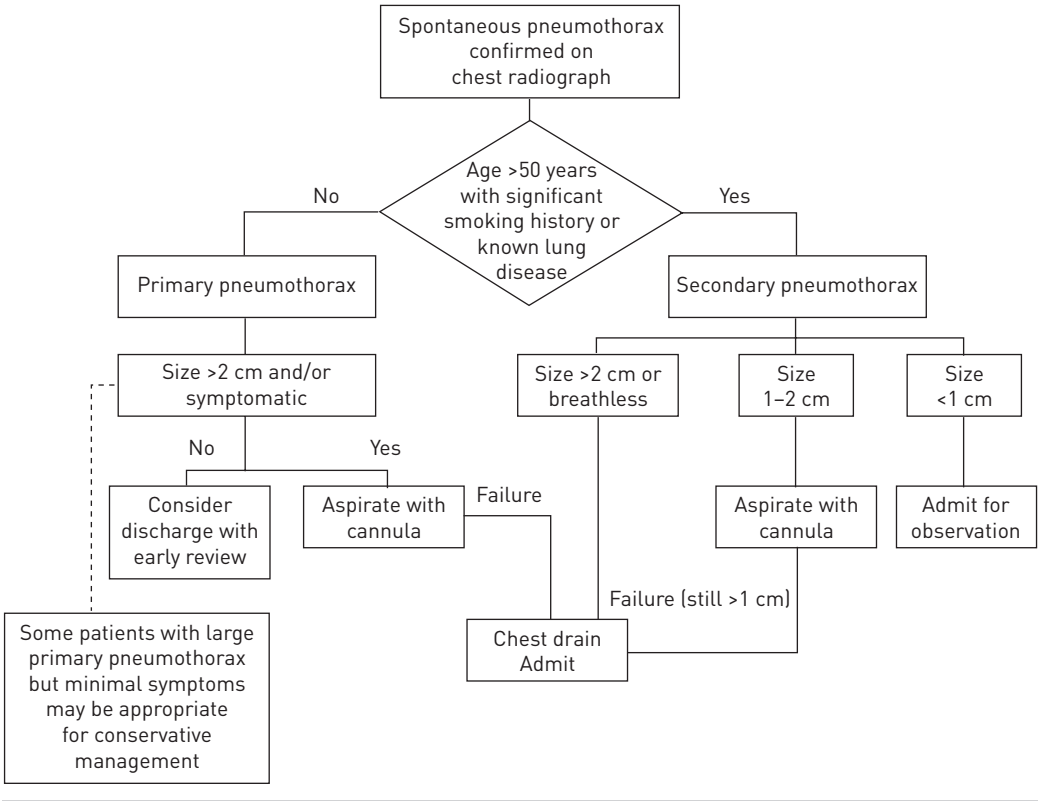

Figure 3. Pneumothorax management flow diagram. Reproduced and modified from [3] with permission.

pneumothorax. The ACCP suggests >3 cm from the apex of the hemidiaphragm to the cupula [2]. The BTS definition is >2 cm from the lung margin to the chest at the level of the hilum (figure 3) [3].

The BTS suggests that if the pneumothorax is large or the patient is symptomatic, simple aspiration should be attempted. If this does not succeed, the clinician should proceed to chest tube insertion, with a recommendation that a small-bore (<14-French) Seldinger chest drain should be used (figure 3) [3]. The ACCP advocates proceeding directly to chest tube insertion [2]. The rationale behind the BTS guidance comes from studies [30, 31] and meta-analyses [32–34] that suggested that simple aspiration was as successful as a chest drain in treating pneumothorax, and led to fewer bed days. It is recommended that if >2.5 L of air is removed *via* simple aspiration, then the physician should proceed to a chest tube, as there is likely to be a persistent air leak [3].

The guidance for SSP is similarly based on the size of the pneumothorax and symptoms. Symptomatic patients or patients with large pneumothoraces should have a chest tube inserted. The BTS suggests that if a patient is asymptomatic and the pneumothorax is between 1 and 2 cm, simple aspiration can be attempted. If the pneumothorax is smaller than 1 cm, admission with observation is recommended (figure 3) [3].

Managing a persistent air leak and failure to re-expand

Suction

The routine use of early suction is not recommended by the BTS guidelines [3]. A small RCT found no significant difference in the rate of lung re-expansion or duration of hospital stay with suction compared with no suction [35].

There may be a role for the use of high-volume, low-pressure suction in a persistent air leak (arbitrarily defined as continuous bubbling for >48 h after chest drain insertion) or incomplete re-expansion of the lung, with the theory that the air may be removed from the pleural cavity at a greater rate than it enters *via* the visceral membrane. The use of suction too early can precipitate re-expansion pulmonary oedema, particularly if the pneumothorax has been present for more than a few days. High-pressure, high-volume suction may lead to perpetuation and/or worsening of the air leak [3]. The typical pressure used is between -10 cmH_2O and -20 cmH_2O.

Surgery

In cases of a persistent air leak or failure of the lung to re-expand after 3–5 days, the BTS recommends that a thoracic surgical opinion should be sought.

The timing of surgical intervention is debated. A study by Chee *et al.* [36] showed that 100% of PSPs and 79% of SSPs with a persistent air leak of >7 days treated with an intercostal drain resolved by day 15 and day 14, respectively, with no mortality. However, surgery carries a low morbidity risk and has good success rates.

There are two main types of surgery, thoracotomy and VATS, with both performed under general anaesthetic. There are several approaches to thoracotomy: the standard posterolateral thoracotomy or methods using a smaller incision, such as axillary thoracotomy, anterior thoracotomy or various mini-thoracotomies [15]. The procedure consists of excision of blebs

and bullae, usually *via* stapling and treatment of smaller bullae with an electrocoagulant or laser [15]. Usually, the surgeon will perform pleurodesis, either by a parietal pleurectomy or by mechanical abrasion of the parietal pleura with gauze. Some surgeons perform chemical pleurodesis. VATS is performed under general anaesthetic with single-lung ventilation. Generally, three ports, a thoracoscope and two lung graspers, are inserted, with the patient in the lateral decubitus position. The same intrathoracic procedure can be performed by VATS as *via* an open thoracotomy [15].

Analysis of RCTs has demonstrated an equivalent success rate between VATS and thoracotomy, with a reduction in analgesia and shorter hospital stays in the VATS cohort [37]. An RCT comparing mini-thoracotomy with VATS showed equivalent reoccurrence rates (2.7% and 3%, respectively) and postoperative pain, with VATS associated with greater patient satisfaction [38]. A recent large prospective cohort study of 1415 patients undergoing VATS with talc poudrage found a recurrence rate of 1.9% and a complication rate of 2% [39]. Interestingly, the recurrence rate was much higher in smokers (4.2%) compared with nonsmokers (0.2%) [39].

Accepted indications for surgical advice are shown in table 1.

Pleurodesis

Pleurodesis by chemical irritant, mechanical abrasion or parietal pleurectomy aims to achieve adherence of the pleural membranes by promoting inflammation. Chemical pleurodesis by a sclerosing agent can be delivered by chest tube, medical thoracoscopy or VATS.

Chemical pleurodesis with intrapleural administration *via* a chest tube has been investigated with several agents, including antibiotics (minocycline, tetracycline and doxycycline) and talc preparations. It is a suitable option for patients who would be ineligible or unwilling to have surgery, after assessment by a respiratory specialist. It has been suggested that chemical pleurodesis is an easy, safe and cost-effective method for the treatment of spontaneous pneumothorax and could be considered as an initial treatment of PSP [40]. It has the advantage of being able to be administered by the bedside; however, there are potential drawbacks of uneven distribution of talc and the potential for only localised pleurodesis at the site of administration [4]. An RCT investigating the use of minocycline pleurodesis *via* chest drain *versus* chest drain with no pleurodesis in patients with PSP showed lower recurrence rates of 29.2% in the minocycline pleurodesis arm *versus* 49.1% in the control group [41]. However, it has been noted by others that this trial had a high recurrence rate in the control group compared with other studies and compared unfavourably with surgical options [42].

Talc delivered by medical thoracoscopy under direct vision has good long-term success rates. In an RCT in patients with PSP, talc poudrage medical thoracoscopy had a lower

Table 1. Indications for surgical opinion in the management of pneumothorax [3]

Second ipsilateral pneumothorax
First contralateral pneumothorax
Synchronous bilateral spontaneous pneumothorax
Persisting air leak (despite 5–7 days of chest tube drainage) or failure of lung re-expansion
Spontaneous haemothorax
Professions at risk (aircraft personnel, divers)
Pregnancy

recurrence rate when compared with chest tube alone (5% *versus* 27%, respectively) and was more cost-effective [43].

Prevention of recurrence and risk stratification

As mentioned in the previous section, surgery and talc poudrage have both been shown to dramatically reduce recurrence. The decision to perform a definitive invasive procedure is based on the risk of recurrence, and the potential consequences if one occurs. Currently, most centres wait until the second presentation of PSP before considering definitive management, although it is often considered earlier in patients with SSP, due to the potentially life-threatening risk of a recurrence. However, the decision is made difficult because of a wide range in the quoted recurrence rates from 13.5% to 54% [41, 44, 45] and limited data on how individual risk factors affects this. The studies examining recurrence have used differing methodologies and include epidemiological and prospective randomised studies with various inclusion criteria, timescales and definitions of recurrence. In a recent prospective cohort study of 234 consecutive patients with their first episode of PSP who were admitted and treated conservatively with a chest tube, recurrence was observed in 54% of patients, with 30% of these patients experiencing a pneumothorax in the contralateral lung [46]. Conversely, a recent epidemiological study of 246 534 episodes of spontaneous pneumothorax (PSP and SSP) in the UK found a 13.5% risk of recurrence requiring readmission to hospital within 1 year [45]. Studies looking at SSP have found that 40–50% of patients will have a second pneumothorax if pleurodesis or definitive thoracic surgery is not performed [47]. The rate of pneumothorax is also thought to increase with every subsequent recurrence. A study from 1963 found that the risk of recurrence was 57% after the first pneumothorax, 62% after the second and 83% after the third [48]. However, this was only statistically significantly different between the first and third recurrence [49].

One of the aims in the management of pneumothorax should centre on the identification of patients likely to have a recurrence and hence who may benefit from early surgery. Height in men, female sex and low bodyweight are associated with an increased rate of recurrence [44, 46]. Smoking is associated with a high risk of recurrence, with smoking cessation after an initial PSP associated with a relative risk reduction of >40% [44]. As the rupture of blebs or bullae is thought to be the main cause of PSP, studies have looked into whether radiology can help in predicting the risk of reoccurrence, providing conflicting answers. A prospective study by Martínez-Ramos *et al.* [50] of 55 patients could not demonstrate that the presence, size or number of bullae on CT scans had any influence on recurrence rate. A subsequent study using high-resolution CT on 176 patients with PSP found that the risk of reoccurrence was significantly related to the presence of blebs or bullae, or both [51]. Another study looked at the role of the chest radiography in determining the reoccurrence risk. They looked for radiological abnormalities on the chest radiograph including pleural thickening, blebs/bullae, pleural irregularities and pleural adhesions. They found that the presence of an abnormality (irrespective of type) increased the likelihood of recurrence, and the risk of recurrence increased with each additional abnormality. They recommended surgical pleurodesis for the first episode of PSP when multiple chest radiograph abnormalities are identified at the time of diagnosis [52].

Follow-up

The BTS guidelines recommend that all patients discharged after admission for pneumothorax should be given verbal and written advice about re-presentation if they develop further

symptoms [3]. They should be followed up by a respiratory physician to ensure resolution, institute optimal care of underlying lung disease, explain the risk of recurrence and discuss the possible future need for surgical interventions, as well as re-emphasising lifestyle advice, such as smoking cessation and air travel. Air travel is advised against until 1 week after full resolution of the pneumothorax [3].

Tension pneumothorax

Tension pneumothorax is an uncommon, life-threatening emergency. It can be defined in various ways [53]: 1) clinically, in terms of haemodynamic compromise improved by decompression; 2) in terms of pleural pressures, with ipsilateral pleural pressures exceeding atmospheric pressure; or 3) radiographically, with signs of mediastinal shift (although this can also present in nontension pneumothorax).

Tension pneumothorax occurs from a pleural defect forming a one-way valve system in the pleural membrane, with air entering the pleural cavity on inspiration but unable to exit on expiration. It can arise in a wide range of clinical situations, including ventilated patients, trauma, cardiopulmonary resuscitation, patients with acute exacerbation of lung disease, blocked chest drains and patients receiving NIV. It rarely occurs in PSP [3].

The patient is often very symptomatic and in haemodynamic compromise, with decreased air entry the most common sign (in 50–75% of patients). Trachea deviation away from the affected lung, hyperresonance, hypomobility and hyperexpansion occur less frequently [3]. It is important to recognise the potential differences in clinical presentation in ventilated and nonventilated patients [3]. Diagnosis of tension pneumothorax in ventilated patients requires a high index of suspicion. Its presentation, however, is more consistent than in awake patients, usually presenting with a sudden fall in S_{pO_2}, followed by hypotension over a few minutes [53], with tachycardia, decreasing cardiac output, increased inflation pressures and ultimately cardiac arrest [3].

Awake patients show a greater variability of presentation. They manifest compensatory mechanisms and generally have progressive respiratory deterioration with final respiratory arrest. The time lag from initial symptoms or thoracic insult to diagnosis ranges from a few minutes to >16 h [53].

A chest radiograph is not usually useful and can be misleading, with the size of the pneumothorax and mediastinal displacement not correlating with the degree of tension [3].

The management is high-flow oxygen and prompt emergency needle decompression in the mid-clavicular line, second intercostal space, which is recommended prior to a chest radiograph. A large study found that the mean chest wall thickness of 2574 healthy volunteers, as determined by magnetic resonance imaging, was 5.7 cm on the right and 5.5 cm on the left side in the mid-clavicular line, second intercostal space [54], suggesting that a 7-cm needle may be required [54]. A review article on tension pneumothorax recognised that the standard 14-gauge (4.5 cm) cannula may not be long enough to penetrate the parietal pleura in up to one-third of trauma patients, leading to treatment failure and diagnostic confusion [53]. The use of a trocar instead (7 cm) may negate this problem and prevent kinking. The BTS recommends that if needle decompression is not possible in the second intercostal space, the chest wall may be less deep in the fourth and fifth interspace

and may provide an alternative [3]. This should be followed by a chest tube, with the cannula left in place until bubbling is confirmed with an underwater seal system [3].

Novel management strategies

Ambulatory conservative management

Conservative management is recommended for patients with a small asymptomatic PSP by the BTS [3]. The guidelines do suggest that selected asymptomatic patients with a large PSP may be managed by observation alone. It has been hypothesised that the collapsed lung is more likely to heal, allowing apposition of the visceral leak sites [55]. This is currently under investigation by a multicentre RCT in Australasia, which has been set up to compare ambulatory conservative management with standard management in asymptomatic patients with large pneumothoraces (Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), trial number ACTRN12611000184976).

Use of a Heimlich valve and pleural vents

A Heimlich valve is a one-way valve system that can be attached to a chest tube to enable ambulatory drainage for a patient. Their use has been evaluated in small RCTs and case series, and was subject to a recent literature review (1235 cases in total), which concluded that a Heimlich valve may have benefits for patients' comfort, mobility and avoidance of hospital admission, with comparable outcomes to other current practices, with serious complications being rare [56].

A recent study evaluated their use in patients with iatrogenic pneumothorax following lung biopsy [57]. In patients with a large or symptomatic pneumothorax at 30 min post-biopsy, an enlarging pneumothorax at 60 min, or a persisting or symptomatic pneumothorax, an 8-French drain was inserted and connected to a Heimlich valve chest drain (HVCD). There were no major complications, but eight of the 52 patients developed HVCD-related pleuritic pain, which was successfully managed with 10 mL of intrapleural 0.5% bupivacaine. All patients had their HVCD removed within 48 h. These results are encouraging but may not translate to primary pneumothoraces.

The use of ambulatory pleural vents (figure 4) for the treatment of PSP is currently under evaluation in a randomised multicentre trial for PSP (ISRCTN Registry (www.isrctn.com), trial number ISRCTN79151659). An RCT on their use in SSP is about to commence shortly (Hi-SPEC trial).

Endobronchial valves

Endobronchial valves, more commonly used as an alternative to lung reduction surgery in emphysema, have been used in patients with pneumothorax and a persistent air leak who were deemed not fit for surgical management. These one-way valves are inserted *via* bronchoscopy and aim to obstruct the bronchial airway, resulting in atelectasis of the distal lung, while still allowing drainage of secretions. The largest study into this was a retrospective, nonrandomised study in 40 patients with pneumothoraces (iatrogenic, PSP and SSP), and demonstrated that 19 patients (47.5%) had complete resolution of an acute air leak,

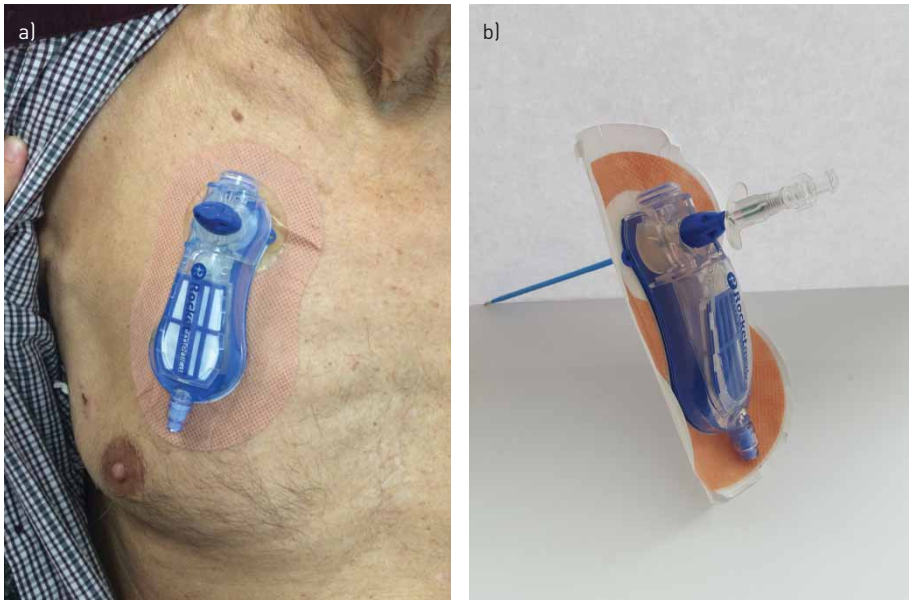

Figure 4. a) Pleural vent in a patient with secondary spontaneous pneumothorax. b) Pleural vent with safety insertion needle *in situ*.

18 patients (45.0%) had a reduction and two patients (5.0%) had no change in air leak status [58]. The remaining patient had no reported outcome.

Air leak monitoring system

Digital drainage systems have been used to allow real-time, continuous quantification of air leaks (figure 5). They have been studied in post-lobectomy chest drains, with several studies showing a reduction in chest drain duration in patients with digital monitoring of air leaks compared with a traditional protocol of using visual and subjective assessment of air leaks

Figure 5. Digital air leak monitoring system (Thopaz Digital Chest Drainage System; Medela Inc. Healthcare, McHenry, IL, USA).

(bubbles) [59–61]. This was contradicted by a more recent study, which showed no change in chest drain duration [62]. However, there are no published studies to date looking at the digital assessment of air leaks in medical patients with PSP or SSP, and caution must be used in applying post-surgical data, whose outcome was chest drain duration. It has been reasonably suggested that digital assessment is a more accurate way of quantifying the air leak than visual inspection of air bubbles in the chest drain bottle. It may allow earlier identification of patients whose leak is not settling and would benefit from early thoracic surgery [4].

Conclusion

Pneumothoraces are a relatively common medical condition that can present as a medical emergency. Any physician managing acute medical patients should be aware of the current treatment algorithms and the factors that influence them, as well as how to identify a life-threatening tension pneumothorax. A greater understanding of the underlying pathophysiology and risk factors involved in the development and formation of pneumothoraces will hopefully enable a more personalised management plan. Newer therapeutic options may enable alternative management pathways for low-risk and ambulatory patients.

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Chapter 2

Pulmonary embolism

Stefano Barco[1] and Stavros V. Konstantinides[1,2]

Pulmonary embolism (PE) is a significant contributor to global disease burden. The presence and severity of right ventricle (RV) dysfunction is a key determinant of the patient's prognosis in the acute phase. Accordingly, risk-adapted treatment strategies have been developed and continue to evolve, tailoring initial management to the clinical presentation and the functional status of the RV. Beyond pharmacological and, if necessary, mechanical circulatory support, systemic thrombolysis remains the mainstay of treatment for haemodynamically unstable patients; in contrast, it is not routinely recommended for intermediate-risk PE. Catheter-directed pharmacomechanical reperfusion treatment represents a promising option for minimising bleeding risk; for reduced-dose intravenous thrombolysis, the data are still preliminary. New, non-vitamin-K-dependent oral anticoagulants, directly inhibiting factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran), have simplified initial and long-term anticoagulation for PE, while reducing major bleeding risk. Use of vena cava filters should be restricted to selected patients with absolute contraindications to anticoagulation, or with PE recurrence despite adequately dosed anticoagulants.

Acute pulmonary embolism (PE) (figure 1), in the majority of cases a consequence and a threatening clinical manifestation of venous thromboembolism (VTE), is the third most frequent acute cardiovascular syndrome behind acute myocardial infarction and stroke, and is a major cause of both acute and long-term morbidity and mortality worldwide. In Europe, for example, the annual number of PE-related deaths may exceed 500 000 in the population according to a frequently cited epidemiological model [1]. Depending on clinical severity and the presence of haemodynamic instability at presentation, >30% of the patients suffering acute PE may die within the first 30 days [2], and as many as 30% of survivors may present with VTE recurrence or some sort of chronic disabling symptoms within months or years after the index event [3]. Finally, an unclear proportion of PE patients (between 1% and 9%) will develop, over the long term, a progressive and potentially lethal pulmonary vascular disease termed chronic thromboembolic pulmonary hypertension [3, 4]. Unavoidably, the medical relevance of PE and its continuously growing impact on the health of an ageing, increasingly thrombosis-prone population are also accompanied by the substantial economic burden that the disease imposes on healthcare systems [5]. These facts highlight the priority of developing effective, and more efficient, management strategies for acute PE and its chronic sequelae.

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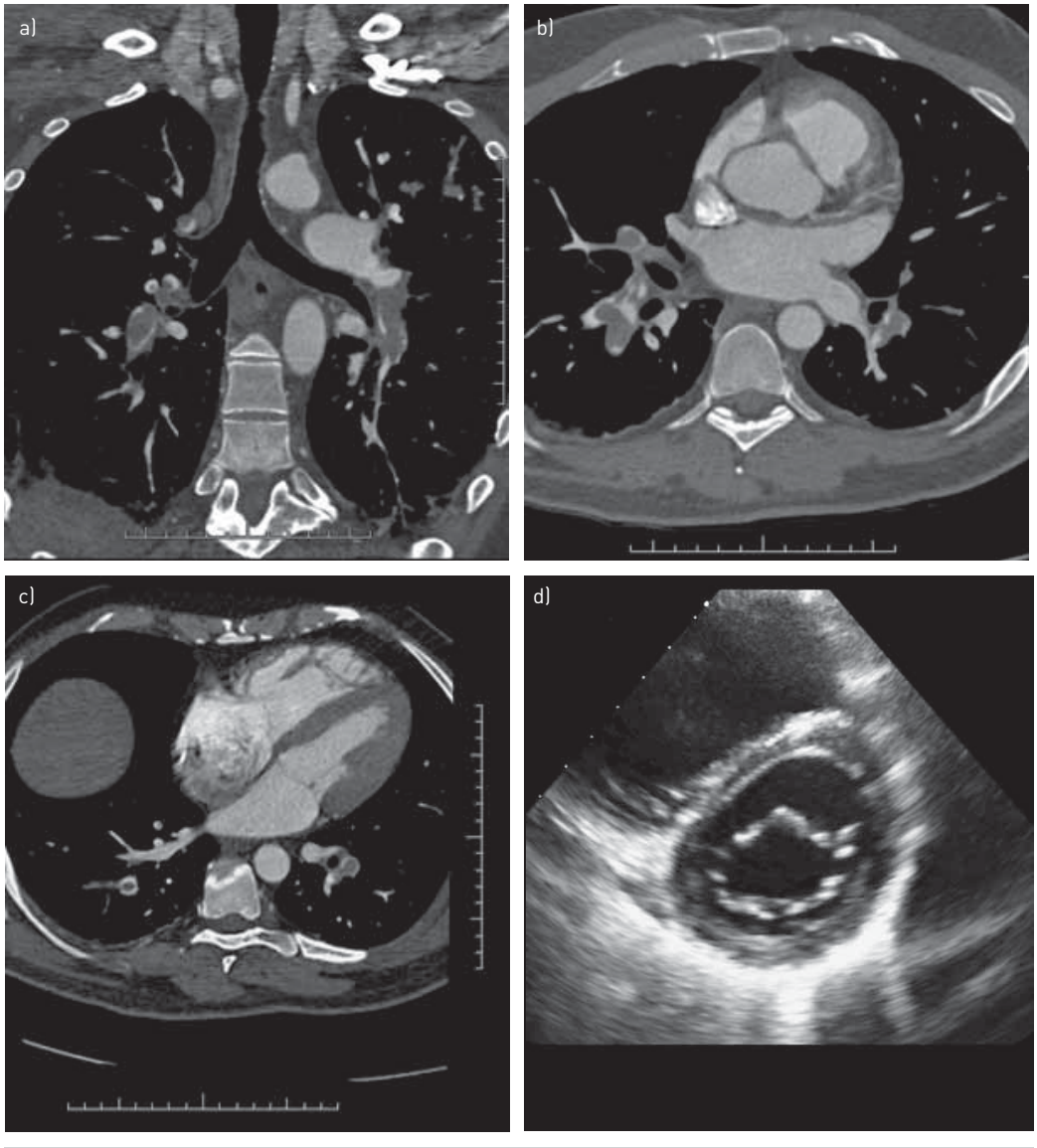

Figure 1. a–c) CT pulmonary angiogram demonstrating bilateral filling defects in the branches of the pulmonary arteries, which are diagnostic of acute pulmonary embolism. a) Coronary plane and b) transverse plane. c) A "four-chamber view" in the transverse plane, which allows a first assessment of right ventricle size, more specifically of the right-to-left ventricle diameter ratio at the tricuspid/mitral annulus level. d) Transthoracic echocardiogram (parasternal short axis view, mitral valve level) demonstrating right ventricular enlargement and a D-shaped left ventricle.

The present chapter focuses on the acute-phase management of PE, viewing it from the angle of medical emergency management. We start by reviewing the progress made recently in risk assessment, which is based on combining clinical findings and the functional status of the right ventricle (RV). Along with general measures for treating overt or impending RV failure, we discuss the evolving, risk-adjusted reperfusion regimens and strategies, focusing on "safer" thrombolysis and other emerging options of catheter-directed treatment. Finally, we elaborate on the current status of, and remaining challenges in,

anticoagulation therapy in the era of non-vitamin-K-dependent, direct oral anticoagulants (NOACs), and describe the use of vena cava filters when anticoagulants are contraindicated.

Risk stratification of patients with acute PE

The optimal management of patients following the diagnosis of acute PE requires the stratification of patients into classes of disease severity in order to adjust the initial treatment to the individual's early death risk [6]. The key determinants of prognosis in the acute phase of PE can be summarised as follows: 1) characteristics of the patient's clinical presentation, including the presence of comorbidities; and, 2) the presence and severity of RV dysfunction, as assessed clinically by echocardiography or CT pulmonary angiography (figure 1), or with the help of laboratory markers, such as cardiac troponins and natriuretic peptides [6]. At the "high" end of the risk spectrum are patients with overt, noncompensated RV failure resulting in reduced cardiac output and manifesting clinically as persistent arterial hypotension accompanied by signs of end-organ hypoperfusion. The patients with high-risk (or "massive", as defined in [7]) PE are those expected to benefit most from immediate reperfusion treatment, combined, if necessary, with circulatory and respiratory support; these measures aim to reduce the RV pressure overload and restore adequate tissue perfusion and oxygenation.

Although high-risk PE patients are undoubtedly the most challenging subgroup, exhibiting 30-day fatality rates of 20–40% or even higher, they represent only ⩽5% of all PE patients [2, 8]. The large remaining group of (apparently) stable, non-high-risk PE patients can be further stratified by employing two categories of clinical tools: 1) the Pulmonary Embolism Severity Index (PESI), or its simplified form (sPESI); and 2) imaging as well as laboratory tests detecting manifest or subclinical RV dysfunction [6]. An updated overview of the imaging and laboratory findings for prediction of intermediate-high risk or intermediate-low risk PE, with the corresponding cut-off values, is provided in table 1.

While PESI and sPESI serve primarily to identify "low-risk" patients who may not require further testing and who may be eligible for early discharge and home treatment, echocardiographic (or CT) or biochemical markers of RV dysfunction represent the key tool for defining the groups of "intermediate-low risk" (with either evidence of RV dysfunction or elevated biochemical markers) or "intermediate-high risk" (with RV dysfunction combined with elevated biochemical markers) (table 2). This advanced classification on the basis of the functional status of the RV helps to determine the duration of haemodynamic monitoring, the need for reperfusion treatment, and the choice of the anticoagulant drug and regimen [6].

Current guidelines do not routinely recommend further risk assessment in patients belonging to PESI class I or II, or with an sPESI of 0, who are considered to be at "low risk" based on large cohort studies. Nevertheless, it is possible that some of these patients will exhibit RV dysfunction on imaging tests and/or elevated biomarker (cardiac troponin or natriuretic peptide) levels in the blood [22]. If any doubts persist regarding the severity and haemodynamic impact of PE on the RV following clinical evaluation of the patient, even in the presence of a formally low PESI or a sPESI of 0, the functional status of the RV should be assessed by imaging and laboratory testing. This does not need to be a complicated or time-consuming procedure: the first important piece of information can be obtained by looking at the size of the RV on CT pulmonary angiography, which is already the current gold standard for confirming acute PE (figure 1). If RV enlargement is then

Table 1. Update on imaging and laboratory tests for prediction of intermediate-high risk or intermediate-low risk pulmonary embolism

Test or biomarker	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	OR or HR (95% CI)	Patients n	Study design [ref.]
Echocardiography	Various criteria of RV dysfunction	74 (61–84)	54 (51–56)	98 (96–99)	8 (6–10)	2.4 (1.3–4.3)	1249	Meta-analysis [9]
CT angiography	RV/LV ⩾1.0	46 (27–66)	59 (54–64)	93 (89–96)	8 (5–14)	1.5 (0.7–3.4)	383	Meta-analysis [9]
	RV/LV ⩾0.9	84 (65–94)	35 (30–39)	97 (94–99)	7 (5–10)	2.8 (0.9–8.2)	457	Prospective cohort [10]
	LA volume ⩽62 mL	NR	NR	NR	NR	2.4 (1.5–3.9)	636	Retrospective cohort [11]
	RA/LA >1.2	NR	NR	NR	NR	2.1 (1.3–3.4)		
	LV ⩽67 mL	NR	NR	NR	NR	1.8 (1.1–3.0)		
BNP	75–100 pg·mL^{-1}	85 (64–95)	56 (50–62)	98 (94–99)	14 (9–21)	6.5 (2.0–21)	261	Meta-analysis [12]
NT-proBNP	600 pg·mL^{-1}	86 (69–95)	50 (46–54)	99 (97–100)	7 (5–19)	6.3 (2.2–18.3)	688	Prospective cohort [13]#
	Various assays/ cut-off values	NR	NR	NR	NR	8.6 (4.1–18.0)	1664	Meta-analysis [14]
Troponin I	Various assays/ cut-off values	NR	NR	NR	NR	4.0 (2.2–7.2)	1303	Meta-analysis [15]
Troponin T	Various assays/ cut-off values¶	NR	NR	NR	NR	8.0 (3.8–16.7)	682	Meta-analysis [15]
	14 pg·mL^{-1+}	87 (71–95)	42 (38–47)	98 (95–99)	9 (6–12)	5.0 (1.7–14.4)	526	Prospective cohort [16]#
	Age adjusted	88 (70–96)	54 (50–58)	99 (98–100)	7 (5–10)	8.7 (2.6–29.3)	682	Prospective cohort [17]
H-FABP	6 ng·mL^{-1}	89 (52–99)	82 (74–89)	99 (94–99)	28 (13–47)	36.6 (4.3–304)	126	Prospective cohort [18]#
		95 (76–99)	59 (52–64)	99 (96–100)	15 (10–23)	26.9 (3.5–203.8)	271	Prospective cohort [19]
	Various assays/ cut-off values	88 (75–95)	70 (65–70)	NR	NR	26.0 (6.6–101.7)	749	Meta-analysis [14]
Copeptin+hsTnT +NT-proBNP	24 pmol·L^{-1}, 14 pg·mL^{-1}, 600 pg·mL^{-1}	73 (48–89)	83 (77–87)	98 (95–99)	20 (12–32)	13.0 (3.9–42.7)	268	Prospective cohort [20]

This table shows the results of meta-analyses or, in the absence thereof, of the largest or relevant prospective cohort studies. In most studies, "early" refers to the in-hospital period or the first 30 days after the index event. NPV: negative predictive value; PPV: positive predictive value; OR: odds ratio; HR: hazard ratio; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; H-FABP: heart-type fatty acid-binding protein; hsTnT: high-sensitivity troponin T; RV: right ventricle; LV: left ventricle; LA: left atrium; RA: right atrium; NR: not reported in the reference cited. #: these studies included only normotensive patients, and used a combined outcome (all-cause death or major cardiovascular complications); ¶: in the studies included in this meta-analysis, cut-off values for the cardiac troponin tests used corresponded to the 99th percentile of healthy subjects with a coefficient variation of <10%; +: high-sensitivity assay. Reproduced and modified from [6] with permission.

detected, the RV status and patient's risk should further be classified based on biochemical tests (circulating cardiac troponins or natriuretic peptides) or, possibly, echocardiographic imaging (table 2).

General management of acute respiratory and right heart failure

The principles of acute right heart failure management were recently reviewed in a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology [23]; an overview of the current treatment options for acute RV failure is provided in table 3.

Hypoxia and hypercapnia caused by acute PE can cause or worsen pulmonary vasoconstriction. Therefore, general supportive care should always be considered. This includes the administration of oxygen therapy to maintain oxygen saturation at >90%, including the use of NIV if standard measures fail in reaching this target. Caution is advised regarding the use of positive-pressure ventilation and intubation with sedation due to their negative effects on cardiac output [23, 24].

Acute RV failure responds principally to changes in pre-load; conversely, excessive volume loading bears the risk of overdistending the RV and consequently increasing wall tension, decreasing contractility, impairing left ventricle filling, and ultimately further reducing

Table 2. Evolving (2014–2016) risk stratification of patients with acute pulmonary embolism

Early mortality risk	Risk parameters and scores			
	Shock or hypotension [#]	PESI class III–V or sPESI ⩾1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High	+	(+)	+	(+)
Intermediate				
Intermediate-high	–	(+)[¶]	+	+
Intermediate-low	–	(+)[¶]	Either one (or none) positive	
Low	–	–	Assessment optional; if assessed, both negative	

+: positive; –: negative; (+): Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock. [#]: based on at least one of the following criteria [21]: 1) need for cardiopulmonary resuscitation; 2) systolic blood pressure <90 mmHg for ⩾15 min; 3) drop in systolic blood pressure by ⩾40 mmHg for ⩾15 min with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL·h^{-1} or mental confusion); 4) need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure of >90 mmHg (including dopamine at the rate of >5 μg·kg^{-1}·min^{-1}). [¶]: Note that current guidelines do not routinely recommend further risk assessment in patients belonging to Pulmonary Embolism Severity Index (PESI) class I or II, or with a simplified PESI (sPESI) of 0, who are considered to be at "low risk" based on large cohort studies. Nevertheless, some of these patients have been reported to exhibit right ventricle (RV) dysfunction on imaging tests and/or elevated biomarker (cardiac troponin or natriuretic peptide) levels in the blood. If any doubts persist regarding the severity of pulmonary embolism upon clinical evaluation of the patient, even in the presence of a formally low PESI or an sPESI of 0, the functional status of the RV should be assessed. If RV dysfunction is then detected, the patient's risk should be classified based on the results of imaging and biochemical tests. Reproduced and modified from [6] with permission.

systemic cardiac output and tissue perfusion. Cautious volume loading guided by central venous pressure monitoring and aimed at maintaining normal central venous pressure values is the appropriate approach.

Beyond volume management, vasopressors and/or inotropes are indicated in acute high-risk PE with haemodynamic instability. Vasopressors, particularly noradrenaline, restore blood pressure and improve cerebral, coronary and other organ perfusion; contrary to widespread belief, pulmonary vascular resistance may not be seriously affected [23, 25]. Dobutamine alone may reduce blood pressure and is therefore usually combined with a vasopressor, such as noradrenaline. Levosimendan combines RV inotropy and pulmonary vasodilation; it is typically preferred over dobutamine in patients with decompensated pulmonary hypertension resulting from left-heart disease, but its place in acute PE is less clear [23]. Phosphodiesterase III inhibitors offer the theoretical advantage of exerting a positive inotrope effect on the RV without deleterious effects on pulmonary vascular resistance. Similar to dobutamine, these drugs may aggravate arterial hypotension and should be combined with noradrenaline if needed. The role of vasopressin in addition to (or instead of) noradrenaline in hypotensive patients is uncertain in the setting of acute RV failure since no data are available; theoretically, its use at a low dosage might be beneficial, since vasopressin promotes pulmonary vasodilation along with being a systemic vasopressor.

Acute mechanical circulatory support of the RV may be required in certain clinical situations including acute PE. Timely implantation is critical in order to avoid potentially irreversible end-organ injury; therefore, early transfer of the patient to an appropriate centre is essential for success. Device selection depends on the anticipated duration of mechanical support. ECMO or extracorporeal life support may find increasing use as short-term mechanical support in the future (table 3) [22].

Reperfusion techniques and regimens for acute PE

Thrombolytic agents have been used for the treatment of acute PE for almost five decades [26]. International guidelines and consensus statements agree that an immediate systemic reperfusion treatment with intravenous thrombolysis represents the mainstay of therapy for high-risk (or "massive") PE [6, 7, 27]. This recommendation is partly supported by meta-analyses of randomised trials, which enrolled >2000 patients with acute PE and indicated that thrombolysis may reduce early mortality or the need for rescue treatment upon decompensation (OR 0.34, 95% CI 0.22–0.52); these beneficial effects appeared to be most prominent in high-risk PE (OR 0.18, 95% CI 0.04–0.79) [28]. However, the main (and difficult to predict) adverse effect of systemic thrombolysis is major bleeding, which occurs much more frequently than under anticoagulation alone (OR 2.91, 95% CI 1.95–4.36), particularly when fatal or intracranial haemorrhage is considered (OR 3.18, 95% CI 1.25–8.11) [29]. In light of this delicate balance, the patient subgroups with the most favourable benefit-to-risk ratio and thus the best candidates for thrombolytic treatment remain rather poorly defined.

An overview of the recommendations for thrombolytic treatment of PE in current evidence-based guidelines is provided in table 4. At present, systemic thrombolysis is indicated only for haemodynamically unstable patients due to the high risk of early death [6, 30], while intermediate-risk patients probably do not benefit from its routine use, and thrombolysis should only be used as a rescue treatment in the case of haemodynamic decompensation under anticoagulation alone [6]. This proposed strategy is based on the results of the

Table 3. Overview of the treatment of acute right heart failure in patients with high-risk pulmonary embolism

Strategy	Properties and use	Caveats
Volume optimisation		
Volume loading, saline or Ringer's lactate, >200 mL per 15–30 min	Consider in patients with decompensated RV failure, normal central venous pressure, low arterial pressure	Volume loading can overdistend the ventricles, worsen ventricular interdependence and reduce cardiac output
Vasopressors and inotropes		
Norepinephrine 0.2–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Increases RV inotropy and systemic blood pressure, promotes positive ventricular interactions, restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine 2–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor, especially if left-heart failure present
Levosimendan 0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$#	Combines RV inotropy and pulmonary vasodilation; favourably affects right ventricular–arterial uncoupling	May aggravate arterial hypotension
Mechanical circulatory support		
ECMO/ECLS	Short-term support, cost-effective and rapid; an oxygenator can be added	Complications with use over longer periods (>5–10 days)
Percutaneous catheter-mounted micro-axial pumps		Limited pump capacity; ECLS preferred in severe cardiogenic shock or where high pump flow required
Paracorporeal RVADs	Appropriate for longer-term use (*e.g.*, weeks or months); can be combined with oxygenators when pulmonary support also needed	

ECLS: extracorporeal life support; RVAD: right ventricular assist device; RV: right ventricle. #: a bolus of 6–12 $\mu g \cdot kg^{-1}$ over 10 min is optional and not recommended if systolic blood pressure is <90 mmHg; infusion can be decreased to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or increased to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Reproduced and modified from [23] with permission.

Pulmonary Embolism Thrombolysis (PEITHO) trial, which compared a single bolus of tenecteplase (plus heparin) with placebo (plus heparin) in 1006 patients with acute PE and RV dysfunction plus myocardial injury, detected by imaging and a positive cardiac troponin test; even in this intermediate-high risk group, the clinical benefits of thrombolysis were offset by the intracranial and other major bleeding risks [32].

The question of whether alternative approaches to reperfusion treatment of PE could achieve comparable efficacy while minimising the bleeding risk associated with systemic thrombolysis remains to be answered. The use of reduced-dose systemic thrombolysis might represent an

option for improving safety while maintaining the efficacy of this treatment. In a preliminary, prematurely terminated trial of 118 patients, who roughly corresponded to the European Society of Cardiology definition of high-risk or intermediate-high risk PE, half-dose recombinant tissue plasminogen activator (rtPA; alteplase) appeared comparable to the full dose in terms of efficacy, and improved safety was suggested [33]. In another study of 121 patients with rather arbitrarily defined "moderate PE", reduced-dose rtPA seemed adequately safe and effective over the long term [34]. These data are hypothesis-generating and are insufficient, at the present stage, to support the use of "low-dose" thrombolytic regimens as an alternative to the dosage approved for systemic (intravenous) use.

Catheter-directed pharmacomechanical reperfusion with low-dose local thrombolysis represents a promising option for clearing pulmonary thrombi from the larger arteries [35]; this procedure is an alternative to operative embolectomy if systemic thrombolysis is contraindicated (table 5) [6]. The phase II Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial enrolled 59 acute PE patients with acute main- or lower-lobe involvement and a right-to-left ventricle dimension ratio of $\geqslant$1.0. The primary objective was to compare unfractionated heparin plus a 15-h catheter-directed, ultrasound-assisted regimen of 10–20 mg rtPA *versus* anticoagulant alone [36]. The intervention led to significant recovery of RV function, indicated by a reduction of the subannular right-to-left ventricle dimension ratio, at 24 h, with no increased risk of major haemorrhage [36]. Supportive of the efficacy and safety of this approach are the results of a prospective, single-arm multicentre trial on 150 patients with submassive or massive PE [37], and those of a registry on catheter-directed, either purely mechanical or pharmacomechanical, thrombus removal including 28 patients with massive PE and 73 with submassive PE [38].

Like any interventional procedure, catheter-directed pharmacomechanical reperfusion requires adequate operator expertise and institutional volume. Furthermore, it remains to be determined whether the speed of thrombus removal, and consequently of the relief of the RV from pressure overload, is adequately high in patients with overt or imminent haemodynamic decompensation, and whether the use of ultrasound is really necessary for obtaining maximum efficacy [36].

Anticoagulant drugs and regimens

In patients with acute PE, early anticoagulant treatment should be initiated to reduce the risk of recurrence and fatal thromboembolic events. In patients undergoing the diagnostic workup for acute PE and classified as having an intermediate or high clinical probability for PE (before imaging tests are performed), anticoagulant treatment with a parenteral agent, preferably subcutaneous low-molecular-weight heparin or fondaparinux, is recommended [6]. Subjects who are candidates for thrombolytic treatment should receive agents with shorter half-lives (unfractionated heparin) and the possibility of laboratory monitoring of their anticoagulant levels.

The standard length of anticoagulation covers a minimum duration of 3 months. For many years, parenteral anticoagulant agents (heparins or the synthetic pentasaccharide fondaparinux) followed by vitamin K antagonists (VKAs) represented the gold standard for the anticoagulant treatment of VTE [39]. The standard regimen consisted of parenteral anticoagulation and VKA co-administration for the first 5–10 days, until the international normalised ratio (INR) values reached the target therapeutic range (INR between 2.0 and

Table 4. Recommendations for systemic thrombolysis in evidence-based guidelines and consensus statements

Guidelines	Population	Recommendations	Strength/ class	Level of evidence
ESC 2014 [**6**]	High-risk PE	Intravenous anticoagulation with UFH to be initiated without delay	I	C
		Thrombolytic therapy	I	B
		Surgical embolectomy for patients in whom thrombolysis is contraindicated or has failed	I	C
		Percutaneous CDT as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed	IIa	C
	Intermediate-high risk PE	Routine primary systemic thrombolysis not recommended	III	B
		Close monitoring to permit early detection of haemodynamic decompensation	I	B
		Thrombolytic therapy in presence of clinical signs of haemodynamic decompensation	IIa	B
		Surgical embolectomy or percutaneous CDT may be considered if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	C
ACCP 2016 [**30**]	With hypotension	In absence of high bleeding risk: systemic thrombolysis	2	B
		In presence of high bleeding risk or if systemic thrombolysis failed: surgical embolectomy	2	C
	Without hypotension	Recommendation against systemically administered thrombolysis	1	B
	Acutely deteriorating during anticoagulation	Systemic thrombolysis	2	C
	Candidate for thrombolysis	Systemic thrombolysis *via* a peripheral vein over CDT	2	C
NICE 2015 [**31**]	Haemodynamic instability	Offer UFH and consider systemic thrombolytic therapy		

Continued

Table 4. Continued

Guidelines	Population	Recommendations	Strength/ class	Level of evidence
	Haemodynamic stability	No systemic thrombolytic therapy		
	USAT *versus* CDT	The evidence on USAT raises no major safety concerns over those of CDT alone; with regard to efficacy, evidence of any enhancement of thrombolysis over CDT alone is inadequate		
AHA 2011 [**7**]	Massive PE[#]	Thrombolysis reasonable for patients with acceptable risk of bleeding	IIa	B
	Submassive PE[¶]	Thrombolysis considered if clinical evidence of adverse prognosis (new haemodynamic instability, worsening respiratory insufficiency, severe right ventricle dysfunction, or major myocardial necrosis) and low risk of bleeding	IIb	C
	Candidates for thrombolysis	Catheter embolectomy and fragmentation or surgical embolectomy for patients with contraindications to fibrinolysis	IIa	C
		Catheter embolectomy and fragmentation or surgical embolectomy for patients who remain unstable after receiving fibrinolysis	IIa	C

ESC: European Society of Cardiology; ACCP: American College of Chest Physicians; NICE: National Institute for Health and Care Excellence; AHA: American Heart Association; PE: pulmonary embolism; UFH: unfractionated heparin; CDT: catheter-directed thrombolysis; USAT: ultrasound-accelerated thrombolysis. [#]: acute PE with sustained hypotension (systolic blood pressure <90 mmHg for ⩾15 min or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolaemia, sepsis, or left ventricle (LV) dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 beats·min^{-1} with signs or symptoms of shock) [7]; [¶]: acute PE without systemic hypotension (systolic blood pressure ⩾90 mmHg) but with either RV dysfunction or myocardial necrosis [7].

3.0) for at least two consecutive days; then heparin was discontinued. This strategy is still valid and is included in the guideline recommendations [6, 30]; however, in the past decade, two classes of NOACs were approved for the treatment and secondary prophylaxis of acute PE: three direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and one direct thrombin inhibitor (dabigatran etexilate). These drugs exhibit similarly short half-lives (7–13 h) and a predictable anticoagulant effect, allowing fixed-dose administration with no need for routine monitoring. Large phase III trials showed that these drugs were non-inferior to standard treatment (heparin followed by VKAs) with

Table 5. Absolute and relative contraindications to thrombolytic therapy

Absolute contraindications	Relative contraindications
Haemorrhagic stroke or stroke of unknown origin at any time	Transient ischaemic attack in the preceding 6 months
Ischaemic stroke in the preceding 6 months	ral anticoagulant therapy
Central nervous system damage or neoplasms	Pregnancy, or within 1 week post-partum
Recent major trauma/surgery/head injury in the preceding 3 weeks	Noncompressible puncture site
Gastrointestinal bleeding within the last month	Traumatic resuscitation
Known bleeding risk	Refractory hypertension (systolic blood pressure >180 mmHg)
	Advanced liver disease

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respect to the efficacy outcomes, while their safety profile was superior to that of the comparator in terms of both total bleeding rates [40] and, possibly, bleeding severity [41, 42]. Table 6 summarises the approved regimens of the NOACs for the initial, long-term and extended management of acute PE.

For specific "vulnerable" patient subgroups, or in specific situations during anticoagulation treatment, adapted regimens or monitoring strategies may be necessary. Table 7 provides an overview of these special conditions with the preferred anticoagulation strategies based on the available evidence and/or expert opinion.

Vena cava filters

Vena cava filters may be considered in selected patients with acute VTE to prevent PE or further PE events and reduce PE-associated mortality. The principal indications for placement of filters in the infrarenal portion of the inferior vena cava are typically considered to be the presence of absolute contraindications to anticoagulant treatment in a patient with acute VTE, and with PE recurrence despite documented adequate anticoagulation [6, 30]. Nevertheless, in some countries, an increasing use of filters has been observed over the past decade [66–68], even in individuals who had no contraindications to anticoagulation (9.6% of all placements according to a recent study [69]). In the USA, the annual rate of vena cava filter placement increased from 19 to 32.5 per 100 000 hospitalisations between 1999 and 2010 ($p<0.001$); among patients hospitalised for (or with) acute PE, the proportion of those who received a vena cava filter increased from 15.8% to 16.4% ($p=0.11$) [67].

The recent Prévention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC 2) trial enrolled hospitalised patients with acute, symptomatic PE associated with lower-limb vein thrombosis and at least one severity criterion. The placement of a retrievable inferior vena cava filter was compared with anticoagulation alone (n=399; randomisation ratio 1:1) [28]. By 3 months, the frequency of recurrent PE was not reduced in the filter compared with the control group (3.0% *versus* 2.0%, respectively; risk ratio with filter 2.0, 95% CI 0.51–7.89); similar results were observed at 6 months [28]. The case against the "liberalisation" of the indications for vena cava filter placement beyond those explicitly

Table 6. Overview of non-vitamin-K-dependent, direct oral anticoagulants in the acute-phase treatment and secondary prevention of venous thromboembolism (VTE)

Anticoagulant	Dosage and interval			Not recommended or contraindicated[#]
	Initial phase	Long-term phase	Extended phase	
Rivaroxaban[¶]	15 mg twice daily for 21 days	20 mg once daily with food (15 mg once daily in VTE patients at higher risk of bleeding (EMA))		CrCl <30 mL·min^{-1} (FDA), or CrCl <15 mL·min^{-1} (EMA); moderate or severe hepatic impairment (Child-Pugh class B and C), or hepatic disease associated with coagulopathy; concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers
Dabigatran etexilate[+]	Initial therapy with parenteral anticoagulation for 5–10 days	150 mg twice daily (110 mg twice daily in VTE patients at higher risk of bleeding due to interfering co-medications (EMA))		CrCl <30 mL·min^{-1}; concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL·min^{-1}; concomitant treatment with P-gp inducers (*i.e.* rifampin)
Apixaban	10 mg twice daily for 7 days	5 mg twice daily	2.5 mg twice daily after ⩾6 months of treatment	CrCl <15 mL·min^{-1}; severe hepatic impairment (Child-Pugh class C), or hepatic disease associated with coagulopathy; strong dual inhibitors or inducers of CYP3A4 and P-gp
Edoxaban[§]	Initial therapy with parenteral anticoagulation for 5–10 days	60 mg once daily; 30 mg once daily can be considered in patients with one or more of the following factors: CrCl 15–50 mL·min^{-1}; body weight ⩽60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin or ketoconazole		CrCl <15 mL·min^{-1}; moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy; concomitant treatment with rifampin

This table displays drugs and regimens on the basis of US Food and Drug Administration (FDA) approval for the treatment of acute VTE. EMA: European Medicines Agency; CrCl: creatinine clearance; P-gp: P-glycoprotein; CYP3A4: cytochrome P450-3A4. [#]: all mentioned anticoagulant agents should also be avoided in patients: 1) for whom thrombolysis or pulmonary embolectomy may be required; 2) requiring dialysis; 3) at significant risk of bleeding; 4) receiving a concomitant anticoagulant; 5) with known hypersensitivity to the agent; and 6) during pregnancy or breastfeeding. [¶]: according to the EMA product information, rivaroxaban 15 mg should be considered for the long-term phase if the patient's assessed risk for bleeding outweighs the risk for recurrent VTE; in the European Union, rivaroxaban is contraindicated in patients with CrCl <15 mL·min^{-1} and should be used with caution in patients with CrCl 15–30 mL·min^{-1}; [+]: according to the EMA product information, dabigatran etexilate is not recommended in patients with elevated liver enzymes more than twice the upper limit of normal or with liver disease expected to have any impact on survival, while dabigatran etexilate 110 mg twice daily can be considered in selected patients at higher risk of bleeding; [§]: although a separate extension trial was not conducted for edoxaban, >40% of patients included in the Hokusai-VTE (Edoxaban *versus* Warfarin for the Treatment of Symptomatic Venous Thromboembolism) trial received an extended treatment with edoxaban for up to 12 months. Reproduced and modified from [39] with permission.

Table 7. Preferred anticoagulation regimens in specific subgroups of patients with pulmonary embolism

Group/condition	Chronic oral anticoagulation [#]	References [¶]
Demographic challenge		
Elderly (>75 years; see below for comorbidity, particularly renal dysfunction)	NOAC; VKA	[43, 44]
Children[+]	Heparin, VKA	[45, 46]
Patients living in geographically remote or barely accessible areas, with inflexible work schedule, or with poor INR control	NOAC	[47]
Acute or chronic comorbidity		
Extreme obesity (BMI >40 $kg \cdot m^{-2}$)	Heparin (adjusted dose, laboratory monitoring), VKA	[48–51]
Stage IV chronic kidney disease (eGFR 15–29 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	VKA; in Europe, reduced dose of factor Xa inhibitors may be considered	[49, 51, 52]
Stage V chronic kidney disease (eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), dialysis treatment	Heparin (adjusted dose, laboratory monitoring), VKA	[49, 52]
Severe liver impairment (Child-Pugh class C)	Heparin (laboratory monitoring with anti-factor Xa activity assay); VKA	[30]
Active cancer[+]	Low-molecular-weight heparin for the first 3–6 months; NOAC	[6, 30]
Heparin-induced thrombocytopenia	Acute treatment: argatroban or danaparoid followed by VKA; rivaroxaban; fondaparinux followed by VKA	[53–56]
	History of heparin-induced thrombocytopenia: NOAC; fondaparinux followed by VKA	[54–56]
Antiphospholipid syndrome[+]	Aspirin plus VKA (or heparin)	[57–59]
Concomitant non-valvular atrial fibrillation	NOAC; VKA	[30, 60]
Concomitant valvular atrial fibrillation or mechanical cardiac valve	VKA	[60, 61]
Concomitant stable coronary artery disease	NOAC; VKA	[30, 60]
	Concomitant treatment with aspirin generally not indicated, and increases bleeding risk	[30, 60]
Temporary or reversible situations		
Pregnancy	Low-molecular-weight heparin (adjusted dose, consider laboratory monitoring)	[6, 57]
Breastfeeding	Low-molecular-weight heparin; VKA	[6, 47, 57]
During and up to 48 h after thrombolytic therapy	Unfractionated heparin infusion	[6, 30]
Time of thrombophilia workup with functional tests	Heparin; if given, VKA must be interrupted for ⩾3 weeks, and NOAC for ⩾48 h	[58, 62]

INR: international normalised ratio; eGFR: estimated glomerular filtration rate; NOAC: non-vitamin K-dependent, direct oral anticoagulant; VKA: vitamin K antagonist. [#]: a semi-colon separates the order of preference; [¶]: also consult product monographs of the individual drugs; [+]: dedicated NOAC trials in these populations are currently ongoing [63–65].

mentioned in current guidelines is further supported by recent large epidemiological studies, which did not observe a reduction in mortality or PE recurrence after filter placement in most of the evaluated subgroups [67, 69]. In this context, it should also not be forgotten that the procedure may be complicated by penetration of the filter into the vena caval wall or its embolisation to the right heart cavities [70]; it is, in fact, to be expected that the rate of filter-related complications will be much higher under real-world conditions compared with the setting of large prospective trials such as PREPIC 2 [28].

Summary and conclusions

PE is the third most frequent acute cardiovascular syndrome and, as such, is a common medical emergency and a significant contributor to early mortality. Based on the fact that the presence and severity of RV dysfunction is a key determinant of the patient's prognosis in the acute phase, the risk-adapted treatment strategies that are recommended in current guidelines have been developed to tailor initial management to the clinical presentation and the functional status of the RV. Importantly, impending RV failure is not always evident clinically, and very recent observational data suggest that assessment of the RV by imaging modalities or biochemical markers may be necessary, even in some cases in which standardised clinical risk scores such as the PESI suggest a "low" risk. Beyond pharmacological and, if necessary, mechanical circulatory support, systemic thrombolysis remains the mainstay of treatment for haemodynamically unstable patients with "high-risk" PE. However, it has become clear that the (intracranial) bleeding risks of full-dose thrombolysis outweigh its potential clinical benefits in intermediate-risk PE. Catheter-directed and possibly ultrasound-facilitated pharmacomechanical reperfusion treatment represents a promising option for minimising bleeding risk; experience with this method, which continues to accumulate, will contribute to a better understanding of its efficacy and future indications, particularly with regard to patients at intermediate risk. In addition, preliminary data suggest a possible role for reduced-dose intravenous thrombolysis, but this option cannot be recommended before robust evidence has been provided in its favour. New NOACs directly inhibiting factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran) have simplified initial and long-term anticoagulation for PE, while reducing major bleeding risk. Finally, the use of vena cava filters has increased in some countries over the past decade, but recent trial data strongly support the notion that these filters should be restricted to selected patients with absolute contraindications to anticoagulation, or to cases of PE recurrence despite adequately dosed anticoagulants.

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Chapter 3

Right heart failure

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Pulmonary arterial hypertension (PAH) remains a progressive and fatal disease despite the development of specific therapies over the past decades. Right ventricular function of these patients is sustained by a delicate balance between progressively increasing pulmonary vascular resistance and adaptation to right ventricular afterload. The development of acute right heart failure (RHF), which can be precipitated by a trigger factor or the natural worsening of the disease, is associated with a very poor prognosis. Management of RHF in PAH suffers from a lack of clear recommendations and specific clinical trials. It is mainly based on trigger factor identification, fluid volume optimisation and pharmacological support to improve right ventricular function and perfusion pressure. At the same time, specific management of PAH according to the aetiology must be considered to reduce right ventricular afterload. The development of extracorporeal life support and the optimisation of graft allocation rules contribute to improve the outcome of patients with refractory RHF despite optimal medical management.

Pre-capillary pulmonary hypertension (PH) is defined by an increase in mean pulmonary artery pressure ⩾25 mmHg and a normal pulmonary artery wedge pressure ⩽15 mmHg. It can be classified in different subgroups, corresponding mainly to pulmonary arterial hypertension (PAH, group 1 PH), pulmonary veno-occlusive disease (PVOD, group 1′ PH), PH due to chronic lung disease and/or hypoxia (group 3 PH) and chronic thromboembolic PH (CTEPH, group 4 PH). Haemodynamically, PAH is characterised by chronic elevation in pulmonary vascular resistance (PVR) >3 Wood units, which may lead to right heart failure (RHF) and, eventually, to death [1, 2]. Over the past three decades, improved understanding of the pathophysiology of PAH has led to the development of several medications (prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators), thus changing the therapeutic approach to the disease [3]. Despite these advances, PAH remains a progressive and fatal disease [4, 5]. More dramatically, PVOD is a dismal condition,

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which may deteriorate when treated with PAH-targeted therapies [1, 6]. Similarly, a large number of CTEPH patients are still inoperable or present with persistent severe PH despite pulmonary endarterectomy, medical therapy and/or balloon pulmonary angioplasty [1].

The ability of the right ventricle to adapt to the progressive increase in afterload plays a key role in the prognosis of patients suffering from pre-capillary PH. The mechanisms of adaptation are complex and multifactorial. Over the last few years, interest in the evaluation of right ventricular function in PH has progressively evolved and expanded with the use of echocardiography and cardiac magnetic resonance imaging [7]. The main objective is to evaluate the severity of right ventricular dysfunction and to predict the risk of acute RHF, which has been defined as a rapidly progressive syndrome with systemic congestion resulting from impaired right ventricular filling and/or reduced right ventricular flow output [8]. Most often, it is associated with increased right ventricular afterload or preload, and consequent right ventricular chamber dilatation and tricuspid regurgitation [9, 10]. This clinical setting is associated with a very poor short-term prognosis and requires urgent hospitalisation.

The pathophysiology of acute worsening of RHF in chronic pre-capillary PH remains poorly understood, explaining why its optimal management is very challenging for specialised centres. No specific recommendations regarding the medical care of these patients are currently available. The present chapter will report epidemiological data, pathophysiological issues and clinical experience of acute RHF in patients with chronic pre-capillary PH. In addition, current treatment strategies are discussed and available monitoring methods are evaluated.

Epidemiology

No study has focused on the epidemiology of acute worsening of PH. Nevertheless, it is possible to draw information from studies dealing with acute RHF management or recent trials on PAH-targeted therapies.

In their studies on RHF in PAH patients, Haddad *et al.* [11] retrospectively analysed 119 patients experiencing 207 episodes of RHF over a 12-year period. During the same period, follow-up data of 218 PAH patients were registered in their clinic. Huynh *et al.* [12] also described the outcome of 99 PAH patients admitted to the ICU for acute RHF over a 5-year period. More than 900 patients with PH were seen in the outpatient setting during the study period. In their retrospective analysis of PH patients admitted for RHF, Kurzina *et al.* [13] described the evolution of 37 patients experiencing 60 episodes of RHF, while 172 patients were followed during the 3-year study period. According to these studies, the incidence of RHF among PH patients ranges between 2.2% and 7.2%. It has to be emphasised that these studies took place several years ago. Therefore, this may not provide an accurate picture of current RHF in the whole PH population.

The incidence of RHF in PH patients can also be assessed from recent trials on PAH-targeted therapies. These studies enrolled large cohorts of patients. Nevertheless, their investigational nature implied baseline disease and treatment prerequisites, leading to specific patient profiles that may not reflect the general PAH population. Furthermore, the existence of several treatment arms may bias the interpretation of acute RHF rates. The GRIPHON investigators [14] recently described the effect of selexipag in PAH patients. Over the 3 years of the study, 86 (15%) and 123 (21.1%) patients in the selexipag and placebo groups, respectively, were admitted for RHF. In the AMBITION trial testing a combination of ambrisentan and

tadalafil, GALIE *et al.* [15] described 10 (4%) and 30 (12%) patients with RHF in the combination and pooled monotherapy groups, respectively, over a 1.4-year study period. Lastly, the SERAPHIN investigators testing macitentan also found between 8.8% and 17.7% of patients according to the different groups (placebo, macitentan 3 mg or macitentan 10 mg) affected by RHF, syncope or haemodynamic impairment over 3 years [16]. Therefore, although limited by the absence of dedicated studies and constraints pertaining to the design of investigational trials, it can be estimated from the aforementioned data that the annual incidence of RHF in PH patients probably ranges between 2% and 9%. It has to be kept in mind that in most of those studies acute RHF was defined on a clinical and/or echocardiographical basis with heterogeneous definitions of "abnormal" ranges of the registered variables. This further limits the interpretation of acute RHF epidemiology.

Survival

To the best of our knowledge, only seven studies have reported the short-term survival rates of PH patients affected by RHF (table 1) [11–13, 17–21]. It has to be noted that the diagnosis of RHF was mostly based on clinical assessment (dyspnoea, lower limb oedema, diuresis, systemic arterial pressure). Treatment protocols were different among these studies, somewhat limiting the comparisons. The wide range of the reported mortality rates, which varied from 14% to 100%, is likely to be explained by the gap in the severity of illness among studies. The higher mortality rates were described among patients requiring inotropes and vasoactive drugs, mechanical ventilation, and renal replacement therapy. It has to be emphasised that availability and physician skills for both right ventricular assist devices and/or emergency transplantation have considerably increased since the publication of the aforementioned studies. Therefore, recent studies on the outcome of such patients in the era of these new tools are warranted.

One study analysed the prognosis in survivors of a RHF episode. Six out of the 27 patients discharged from the ICU were dead at 3 months. In this study, seven out of the 27 patients discharged were subsequently referred for at least a second time to the ICU for similar symptoms within the 18-month study period [21].

Pathophysiology and clinical features of RHF in pre-capillary PH

The right ventricle is characterised by a thin wall and a complex three-dimensional conformation (unlike the left ventricle), which is appropriate for the low resistance and high compliance found in the pulmonary circulation. The left and right ventricles interact *via* the interventricular septum. Their synchronisation is also aided by the pericardium, which maintains a consistent beat-by-beat intracardiac volume.

In pre-capillary PH, chronic elevation of PVR leads to chronic conformational adaptation of the right ventricle. The objectives of the right ventricular wall changes are to increase contractility and to maintain a preserved systolic and diastolic right ventricular function to optimise ventriculo-arterial coupling despite high levels of PVR. In early stage of the disease, adaptive mechanisms of the right ventricle are mainly characterised by progressive concentric hypertrophy [10]. During this first stage, corresponding to a compensated state, right ventricular function is generally relatively well preserved. With further disease progression, inappropriate adjustment mechanisms develop. Progressive right ventricular

Table 1. Studies reporting short-term right heart failure outcome in pre-capillary pulmonary hypertension patients

	Haddad [11]	Huynh [12]	Kurzyna [13]	Campo [17]	Sztrymf [19]	Jiang [20]	Sztrymf [21]
Design	Single-centre, retrospective	Single-centre, retrospective	Single-centre, retrospective	Single-centre, retrospective	Single-centre, prospective	Single-centre, prospective	Single-centre, prospective
Study period	1997–2009	2004–2009	2005–2007	2000–2009	2011–2012	2009–2010	2005–2007
Patients n	119	99	60	115	53	209	46
Age years	ND	51.9±13.6	47±18	55±15	63.3 (47.8–71.9)	ND	50 (16.2–77.4)
Admission in ICU n	28	99	ND	29	53	ND	46
Inotropic and/or vasoactive drug intake n	32	44	33	35	7	209	46
Mechanical ventilation n	10	34	0	9	0	0	0
Renal replacement therapy n	4	20	0	3	0	0	ND
Length of stay days	9 (2–96)	10 (5–16)	ND	7 (4–12)	5 (3–10)	ND	9 (4–16)
Mortality %							
Whole cohort	38	30.3	31.6	14	17	4.1–14.1[#]	41.3
Patients receiving catecholamines	ND	50	60	45.7	42.8	ND	41.3
Patients undergoing renal replacement therapy	ND	70	NA	ND	NA	ND	NA
Patients undergoing mechanical ventilation	ND	71	NA	100	NA	ND	NA

Data are presented as mean±SD or median (range), unless otherwise stated. ND: not described; NA: not applicable. [#]: according to treatment arm allocation (fasudil or placebo).

dilatation and conformational modifications lead to tricuspid regurgitation, gradual reversal of the septal curvature and, finally, progressive deterioration of right ventricular function [22, 23]. At a certain point, the compensatory mechanisms become insufficient, leading to RHF characterised by the occurrence of symptoms or signs of heart failure. The right ventricular enlargement and septal displacement leads to a reduction in left ventricular preload by reducing venous return and impaired left ventricular diastolic compliance. All of these modifications lead to a fall in cardiac output and subsequent decreased systemic blood pressure, further reducing coronary perfusion of the right ventricle. These changes also impair diastolic heart function, therefore increasing right atrial pressures and, in turn, contributing to impaired liver and/or kidney function [22].

These modifications are the result of complex molecular mechanisms and cellular changes that have been mainly studied in experimental models of RHF. The right ventricular hypertrophy is the result of an increase in both protein synthesis (*e.g.* collagen fibres in the extracellular matrix) and myocardial cell population. A change in contractile protein isoforms has been observed with resultant alteration of cardiomyocyte function [23]. Progressive fibrosis of the extracellular matrix also contributes to maladaptative right ventricular remodelling. The cellular damage leading to a decrease in right ventricular performance is probably promoted by multiple molecular mechanisms, including changes in the neurohormonal system [24], oxidative stress and increased apoptosis [25], and inflammation and disorders of cellular energy metabolism [26].

The ability of the right ventricle to adapt to the modification of afterload varies widely between individuals and according to the aetiology of PH. For example, specific myocardial involvement in scleroderma probably participates in early impairment of right ventricular function and, finally, a poorer prognosis compared with idiopathic PAH or other forms of PH. In contrast, RHF occurs much later in Eisenmenger's syndrome, leading to a better long-term survival. In this setting, the better cardiac adaptation to the pressure overload is promoted by the persistence of a fetal phenotype of the right ventricle that is characterised by right ventricular wall hypertrophy. Moreover, the right–left shunt leads to ventricular offloading [27].

There is currently no clear clinical definition that allows us to differentiate between right ventricular dysfunction and RHF. RHF can present with a wide range of symptoms, which are very heterogeneous in terms of severity. The insidious onset of exercise incapacity and fatigue are already the result of decreased systolic reserve or low cardiac output. Diastolic RHF leads to gradual fluid retention, which can be translated into peripheral oedema, ascites or anasarca. Finally, impaired right ventricular function and dilatation of the right-sided cavities promote the occurrence of supraventricular and ventricular arrhythmias causing palpitations and some cases of sudden death. Some authors consider that the appearance of any of these symptoms, whatever the severity, is already the manifestation of deleterious adaptive phenomena and therefore of RHF [22].

All patients suffering from pre-capillary PH, and especially the patients suffering from PAH, PVOD or CTEPH, may suffer from an acute exacerbation of RHF as the disease progresses, characterised by the onset of clinical features of rapidly worsening right ventricular insufficiency. This setting can be promoted by a triggering factor or can just be a manifestation of disease progression. In some cases, RHF leads to the diagnosis of pre-capillary PH. As acute worsening of RHF is associated with a very poor short-term prognosis, it requires urgent care, most often in the ICU.

Management of RHF in patients with chronic pre-capillary PH

Management of RHF in patients suffering from chronic pre-capillary PH is mainly based on trigger factor identification, right ventricular afterload improvement, fluid volume optimisation and pharmacological support to improve right ventricular function. In the case of refractory RHF despite optimal medical management, the only option is lung or heart–lung transplantation (HLT) with the use of extracorporeal circulatory support (ECLS) as a bridge to transplantation (figure 1).

Identification and management of a possible RHF trigger factor

A trigger factor for RHF was identified in ~40% of cases in French patients [21]. In chronic pre-capillary PH, right ventricular function is sustained by a delicate balance between progressively increasing PVR and adaptation to right ventricular afterload (*e.g.* myocardial hypertrophy). All external factors leading to a destabilisation of this balance can precipitate RHF. The identification and specific management of such a trigger factor is essential to increase the chance of right ventricular function recovery and to improve the prognosis of patients.

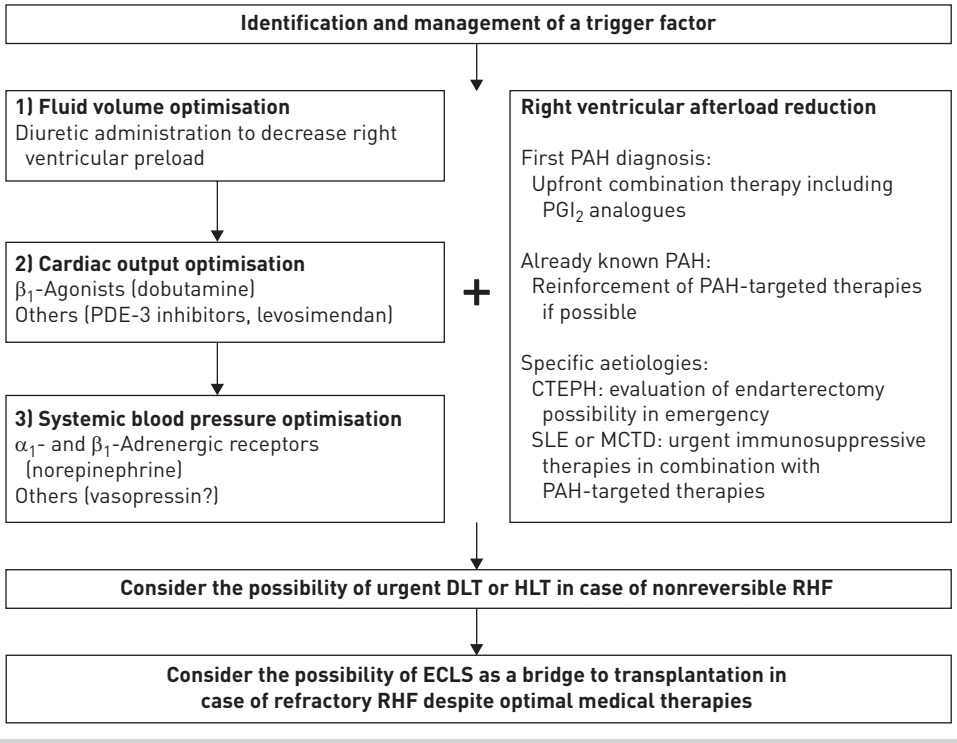
Identification and management of a trigger factor
1) Fluid volume optimisation
Diuretic administration to decrease right ventricular preload
2) Cardiac output optimisation
β1-Agonists (dobutamine)
Others (PDE-3 inhibitors, levosimendan)
3) Systemic blood pressure optimisation
α1- and β1-Adrenergic receptors (norepinephrine)
Others (vasopressin?)
+
Right ventricular afterload reduction
First PAH diagnosis:
Upfront combination therapy including PGI2 analogues
Already known PAH:
Reinforcement of PAH-targeted therapies if possible
Specific aetiologies:
CTEPH: evaluation of endarterectomy possibility in emergency
SLE or MCTD: urgent immunosuppressive therapies in combination with PAH-targeted therapies
Consider the possibility of urgent DLT or HLT in case of nonreversible RHF
Consider the possibility of ECLS as a bridge to transplantation in case of refractory RHF despite optimal medical therapies

Figure 1. Right heart failure (RHF) management in patients with chronic pulmonary hypertension. RHF in pulmonary arterial hypertension (PAH) is mainly based on trigger factor identification, fluid volume optimisation and pharmacological support to improve right ventricular function and perfusion pressure. At the same time, specific management of PAH according to the aetiology must be considered to reduce right ventricular afterload. Extracorporeal life support (ECLS) must be considered as a bridge to transplantation in patients with refractory RHF despite optimal medical therapies. PDE-3: phosphodiesterase 3; PGI_2: prostaglandin I_2; CTEPH: chronic thromboembolic pulmonary hypertension; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease; DLT: double-lung transplantation; HLT: heart–lung transplantation.

Various causes can be identified. Among them, supraventricular arrhythmias (tachyarrhythmia, atrial fibrillation or atrial flutter) are frequently observed in pre-capillary PH and identified as independent risk factors for death [28]. Impairment of atrial function may cause or precipitate RHF in patients with severe haemodynamics at baseline. There is no consensus on the management of supraventricular arrhythmias in PH. However, there are some important points to note. Regarding the use of antiarrhythmic agents, β-blockers and calcium channel blockers should be avoided in this setting because of their deleterious effects on right ventricular inotropic function [29]. The use of digoxin is generally favoured initially for its bradycardic effect [30]. Following this, the priority must be to reverse arrhythmias under anticoagulant cover to improve overall cardiac function. In case of atrial fibrillation, amiodarone is the preferred antiarrhythmic agent. This drug is generally well tolerated, but its long-term safety has never been properly studied in PH [28, 31, 32]. Direct current cardioversion is generally restricted to patients at imminent risk of death and avoided in other conditions due to the high risk of sedation in patients with RHF. In the case of persistent atrial flutter or atrial tachycardia, radiofrequency ablation must be considered [31].

The identification of an infectious aetiology on admission or during hospitalisation is associated with a poor prognosis in comparison with other trigger factors [21]. The gateway of infection is not always identified and may correspond in some patients to bacterial translocation prompted by low cardiac output and increased venous pressure. In patients treated with intravenous epoprostenol, indwelling catheter infection must be systematically screened even if no fever is observed at admission. Insidious septicaemia can be mainly manifested by RHF [33]. In all cases, management of an infectious trigger should not be delayed because of its negative impact on outcomes in patients with RHF.

Rarely, RHF is associated with acute respiratory distress. Some patients may have profound hypoxaemia during periods of RHF due to reopening of a foramen ovale, or in some particular forms of PAH such as Eisenmenger's syndrome or PVOD. Oxygen therapy is recommended in PAH patients with decompensated RHF to maintain an oxygen saturation >90%. Moreover, achieving adequate arterial oxygen saturation by supplemental oxygen could also contribute to decreasing the PVR. Use of high-flow nasal oxygen therapy in this indication could be an interesting option, but has not yet been evaluated in this setting. In cases of acute respiratory distress related to other causes of PH, such as infectious lung disease, the use of invasive ventilation must be avoided as far as possible because of the high risk of RHF worsening and collapse after intubation [34].

A new thromboembolic event can be another potential treatable trigger of RHF, especially in patients with CTEPH. This possibility must be suggested and investigated according to the clinical probability and the current status of coagulation.

Right ventricular preload optimisation

In physiological terms, cardiac performance depends not only on afterload, contractility and heart rate, but also on right ventricular preload. Recent reviews have highlighted the importance of optimising blood volume and therefore the preload in patients with pre-capillary PH, but also highlighted the small number of studies on this topic [35, 36]. The optimisation of preload should help to decrease the right–left ventricular interdependence, reduce the deleterious effect of the tricuspid insufficiency, and thus improve cardiac function and the overall haemodynamics of these patients. Both hypervolaemia and hypovolaemia can

be deleterious. Indeed, the aim is to find a delicate balance that is often difficult to assess. The best method of monitoring right ventricular preload has not yet been identified. In most cases, right heart decompensation is supported by hypervolaemia. Contrary to acute RHF of a healthy heart, the key to the management is based on the use of diuretics to obtain a negative fluid balance. In some patients with a cardiac output that is not too altered at baseline, the use of diuretics as first-line therapy can be sufficient to improve global cardiac function and reverse right ventricular decompensation. Renal replacement therapy has been suggested as an alternative option in patients with severe metabolic abnormalities or in case of insufficient preload reduction despite optimal medical management. We recently performed a retrospective analysis of PH patients with acute heart failure requiring renal replacement therapy in the ICU. Significant systemic hypotension requiring a therapeutic intervention occurred in roughly half of the sessions. The ICU-related, 1- and 3-month mortality of these patients was 46.7%, 66.7% and 73.3%, respectively [18]. In patients with renal failure due to cardio-renal syndrome despite optimal medical management, the best option is to consider ECLS and urgent lung transplantation or HLT (see below) [37].

Cardiac output optimisation and systemic arterial pressure support

In case of severely altered cardiac function, diuretic treatment can be insufficient to reverse RHF. The diuretic treatment can lead in this case to insufficient diuresis, systemic hypotension and impairment in renal function. In this setting, inotropic agents remain important drugs in the management of severe systolic and diastolic RHF. The main goals of such treatments are to improve cardiac output and then renal perfusion. β_1-Adrenergic agonists remain the inotropic agent of choice for managing RHF. Dobutamine is generally initiated at doses of 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and progressively uptitrated in case of persistent low cardiac output signs. The proposed upper limit for the dose is 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In this dose range, dobutamine could improve right ventricle–pulmonary artery coupling by increasing cardiac output and decreasing PVR [38]. The use of higher doses does not improve cardiac function, but can precipitate decreased systemic vascular resistance, increase PVR and tachycardia. We can observe a large heterogeneity of response to β_1-adrenergic agonists between patients. Recently, pre-clinical studies showed an impairment of inotropic response to β_1-adrenergic receptor agonists due to downregulation and desensitisation of β_1-receptors in right ventricular hypertrophy [39]. It has been suggested that PDE-3 inhibitors or the inodilator levosimendan could be interesting alternative options to dobutamine. However, very little data support this management strategy at present [36, 40, 41].

The combined use of dobutamine and diuretics can precipitate systemic hypotension in the most severe patients. An essential goal in the management of RHF is to restore sufficient systemic arterial pressure to preserve right coronary blood flow and organ perfusion. Norepinephrine is the drug of choice in acute RHF and persistent hypotension despite dobutamine therapy. In addition to its effect on systemic pressure, this drug could also contribute to improve right ventricular function and the right ventricle–pulmonary artery coupling [38]. In contrast, phenylephrine is not recommended due to its potential paradoxical effects, leading to an increase in PVR and decrease in cardiac output [42, 43]. The use of vasopressin in RHF due to pre-capillary RHF is more controversial. At low doses, experimental studies have reported a vasodilator effect of this drug on pulmonary vasculature leading to a reduction in PVR. Some clinical cases of vasopressin use as rescue therapy in PH have been published. At higher doses, vasopressin may in contrast increase PVR and cause adverse myocardial effects [36].

Reduction in right ventricular afterload

When managing such patients, the key is probably to determine the best option to decrease the PVR that is the initial cause of the right ventricular insufficiency. After having stabilised the systemic haemodynamics and restored cardiac function with symptomatic treatment as described above, initiation or optimisation of specific PH treatment must be considered to give these patients every possible way out of this unprecedented situation and to decrease the risk of relapse in the long term.

The first step is to determine the mechanism of PH to consider the different treatment options. In specific cases of CTEPH (group 4 PH), the possibility of a surgical treatment by endarterectomy must be evaluated. The decision regarding surgery must take into account the anatomical location of the pulmonary vascular obstruction, and the correlation between the severity of the pulmonary haemodynamics and the degree of obstruction. When lesions are too distal, the risk of surgery is elevated especially in patients with RHF, and medical treatment and/or balloon pulmonary angioplasty must be considered instead [44].

In all cases of PAH (group 1 PH), the best option to decrease the right ventricular afterload is mainly based on PAH-targeted therapies. As mentioned above, the therapeutic approach to PAH has changed over the past three decades with our improved understanding of the pathophysiology of the disease, which has led to the development of several medications (prostacyclin analogues, endothelin receptor antagonists, PDE-5 inhibitors and soluble guanylate cyclase stimulators) [3]. In large randomised controlled clinical trials, these new treatments produced short- and long-term improvements in various relevant clinical and functional parameters, such as symptoms, exercise capacity, quality of life and time to clinical worsening [3]. When PAH is diagnosed at the stage of RHF with New York Heart Association Functional Class (NYHA-FC) IV dyspnoea, it is now clearly recommended to initiate first-line combination therapy including a prostaglandin analogue by continuous intravenous or subcutaneous perfusion [1]. Recently, initiation of upfront triple therapy in patients with severe haemodynamics at baseline with NYHA-FC III or IV dyspnoea demonstrated dramatically improved haemodynamic and functional status of patients in the short and long term in idiopathic PAH [45]. For patients already treated for PAH, the possibility of strengthening the specific PAH treatment should be considered on a case-by-case basis. If the latter is already optimal, the only option is the possibility of a pulmonary or cardiopulmonary transplant.

PVOD is a dismal condition, which may deteriorate dramatically when treated with PAH-targeted therapies [1, 46]. In this setting, the possibility of double-lung transplantation (DLT) must be considered promptly in the management [6].

We must also not ignore the benefits of immunosuppressive therapy in very specific cases of PAH associated with systemic lupus erythematosus or mixed connective tissue disease. Pulmonary vascular involvement in this setting of autoimmune disease can occur with a subacute evolution and a sudden installation of RHF sometimes associated with pericardial effusion. The immunological tests must be performed systematically in the aetiological investigation of a first presentation with RHF due to PAH. The initiation of treatment with steroids and a cyclophosphamide bolus in the initial phase, in combination with specific PAH therapy, can lead to some spectacular results or even reversal of the pulmonary vascular disease [47, 48].

Lung or heart–lung transplantation and extracorporeal life support

DLT and HLT are well-established and valuable options for patients with end-stage pulmonary PH whose NYHA-FC remains III or IV despite optimal medical treatment [1, 49, 50]. However, data from the International Society for Heart and Lung Transplantation registries showed that the vast majority of PH patients received DLT in recent years [51]. Indeed, in most cases we can observe a progressive reversibility of the myocardial remodelling, leading to a recovery of a normal right and left ventricular function after DLT. RHF occurs frequently in patients listed for DLT or HLT and is associated with a high risk of mortality in the absence of transplantation. To decrease waiting list mortality, most countries have revised their transplant allocation rules over the past decade or so. In the USA, implementation of a lung allocation score algorithm in May 2005 [52] was followed by an increased incidence of transplantation, a decrease in waiting list mortality and better post-transplantation survival in patients with idiopathic PAH [53]. However, waiting list mortality remains higher for idiopathic PAH than for other conditions [54]. In France, patients with RHF due to pre-capillary PH can have national priority access to transplantation for a period of 8 days, renewable once. The initiation of this high allocation programme led to a dramatic decrease in mortality of pre-capillary PH patients on transplant lists [55].

In the case of refractory RHF with secondary organ failure despite optimal medical management as previously described, ECLS must be considered as a bridge to urgent transplantation. ECLS that is most often used in PAH patients with refractory RHF is venoarterial ECMO, which can be set up by femoral insertion in awake patients under local anaesthesia. This device leads to a sudden reduction in right ventricular afterload and a reversal of the circulatory insufficiency. The disadvantages of this device are mainly due to the risk of bleeding or infection and the impossibility of the patient to mobilise with venoarterial ECMO.

The Novalung interventional lung assist (Novalung, Heilbronn, Germany) is less often used mainly because its implementation requires a sternotomy under general anaesthesia. This device leads to an immediate reduction of right ventricular afterload and an increase in left ventricular preload. Blood is pumped from the right ventricle through the Novalung and returns to the left atrium. In our experience, we used the Novalung in patients who failed pulmonary endarterectomy with severe persistent PH precluding weaning from the cardiopulmonary bypass.

These devices have been used successfully as a bridge to transplantation in patients with PH and refractory RHF despite optimal medical management in the ICU [56, 57]. In France, 30% of patients transplanted under the high-priority allocation programme were on ECLS before transplantation. The use of ECLS was, however, reserved for selected patients at risk of imminent death despite inotropic support with dobutamine and norepinephrine. ECLS was not deemed suitable in patients with uncontrolled infection or bleeding.

Balloon atrial septostomy (BAS) has been described as another option to decompress the right heart cavities and increase left ventricular preload, leading to an improvement of cardiac output [58, 59]. Only PH expert centres should perform this procedure, which consists of creating an interatrial right-to-left shunt by graded balloon dilatation. A beneficial effect of BAS in patients in World Health Organization functional class IV with refractory RHF despite optimal medical therapy has been reported. Indeed, BAS can be a possible option as a bridge to transplantation [1, 60]. However, the development of ECLS

combined with urgent transplantation and the inherent risks of the BAS procedure limit its use in current practice.

Monitoring

The appropriate monitoring for this specific subset of patients remains a matter of uncertainty. The ideal tool should be able to provide a reliable, repeatable, noninvasive assessment of both haemodynamic treatment targets and peripheral organ failure. It has to be emphasised that there is little data regarding the ability of the monitoring tools used in the setting of PH worsening to translate into therapeutic modifications such as inotropic or vasoactive agent rate modifications. Nevertheless, monitoring the consequences of cardiac failure appears important in order to balance between metabolic demand and haemodynamic impairment.

Haemodynamic monitoring

Echocardiography is an attractive option. Some variables evaluating right ventricular function are recommended by the European Association of Cardiovascular Imaging [61]. Nevertheless, the precise assessment of right ventricular function remains a challenge and very few data support its reliability in the setting of RHF [35]. This led some authors to question the reliability of this tool in the day-to-day management of RHF in PH patients. Recent work has shown good correlations between isovolumic contraction velocity measured with tissue Doppler imaging and contractile reserve, directly influencing fluid and inotropic management [62]. Right heart catheterisation is a safe investigation when performed in stable patients [63], and remains the gold standard test for the diagnosis and long-term follow-up of PH patients. However, concerns have been raised regarding the efficacy of invasive haemodynamic testing in the setting of RHF in pre-capillary PH patients, with no improvement on outcome or even worsening in specific circumstances [12, 64]. Further data are clearly required to better understand the risk/benefit ratio of right heart catheterisation in this setting. Mixed venous oxygen saturation reflects peripheral oxygen consumption and may be a useful tool in that setting. Nevertheless, great caution must be taken in the interpretation of such variables, as it may be affected by many other factors such as anaemia or left ventricular afterload. Therefore, a low value does not necessarily translate to an inotrope shortage.

Novel devices that use transpulmonary thermodilution-based methods to determine cardiac output have generated considerable interest in the general ICU population. This technology provides information regarding numerous physiological variables, including systemic arterial pressure, cardiac output or stroke volume. This method has not been formally validated in PH patients to date, and right ventricular dilation and tricuspid regurgitation are thought to be major limitations in the reliability of the device. Nevertheless, preliminary data support its reliability in cardiac output estimation [65].

Circulating biomarkers

Some circulating biomarkers have been linked to survival, such as brain natriuretic peptide [17, 21] or troponin [13]. Elevated C-reactive protein (CRP) plasma levels may indicate an infectious process in PAH patients with RHF. Nevertheless, moderately elevated CRP levels are indeed predictors of poor prognosis in acute worsening of pre-capillary PH, even

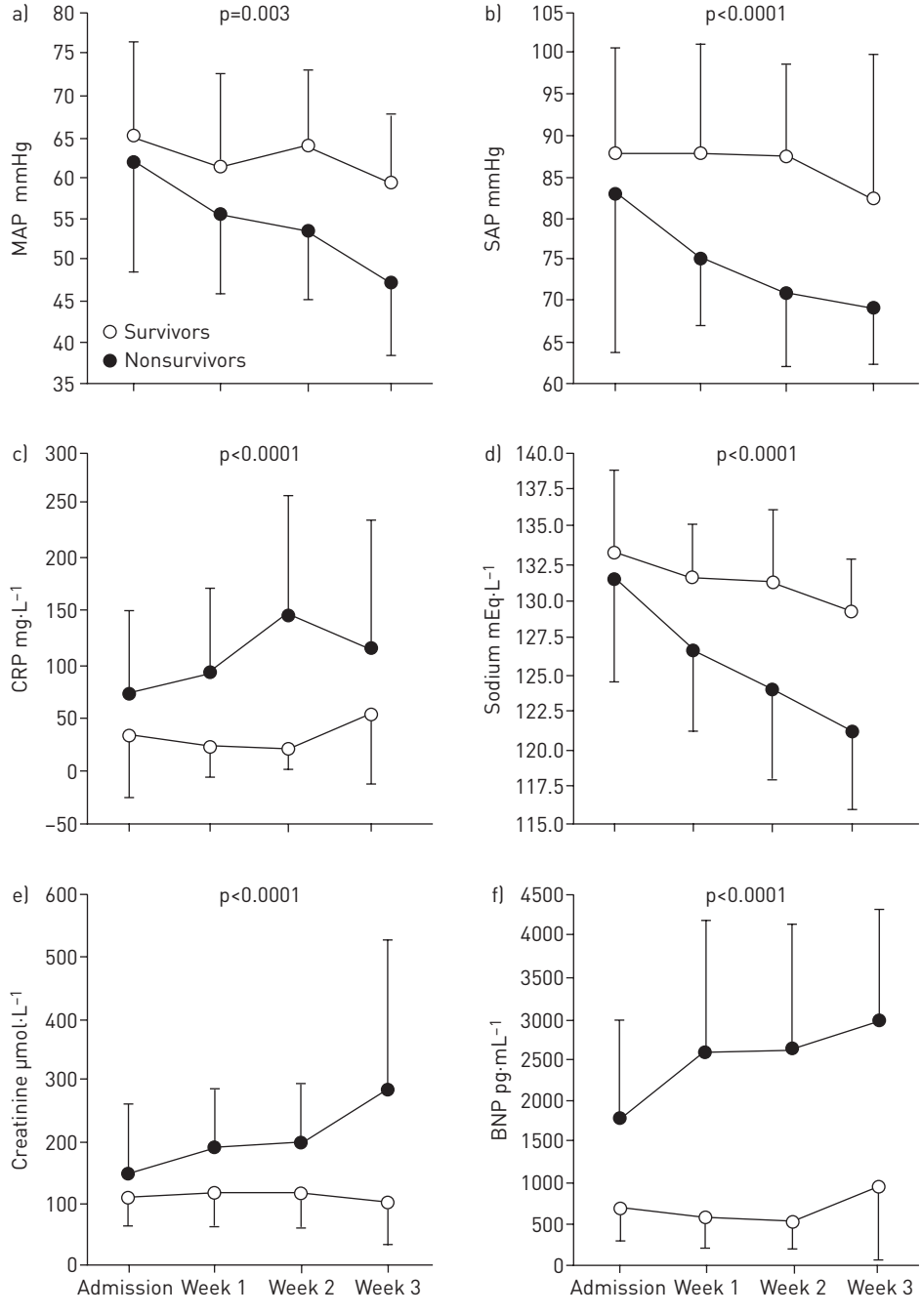

Figure 2. Clinical and biochemical data according to survival in the ICU: patients discharged from the ICU (survivors) or patients who died in the ICU (nonsurvivors). There was a difference in the evolution of some prognostic markers according to the outcome of pulmonary arterial hypertension patients experiencing right heart failure: a) mean arterial systemic pressure (MAP), b) systolic arterial systemic pressure (SAP), c) serum C-reactive protein (CRP) level, d) serum sodium level, e) serum creatinine level and f) serum brain natriuretic peptide (BNP) level. Reproduced and modified from [21] with permission.

without evidence of infection, raising the potential involvement of inflammation among other pathophysiological pathways [21]. Although few studies have assessed the sodium and water regulation imbalance in RHF, it has been documented that hyponatraemia is linked to survival in stable PAH patients [66, 67]. A link between hyponatraemia and survival has also been evidenced in RHF [21].

Although the prognostic value of a single measurement of the aforementioned biomarkers has been found, changes in the values of some of these parameters may predict outcome in the ICU (figure 2) [21]. This could be the basis for future clinical research aiming to better adjust our day-to-day therapeutics on multiple, objective variables.

Peripheral organ status

Peripheral organ involvement is the result of both decreased cardiac output and venous congestion, but may also be impaired by the triggering factor. Therefore, along with the haemodynamic variables, organ function should be assessed regularly to reach a balance between haemodynamic status and peripheral organ demand. Daily monitoring in this setting has already been proposed. The main monitoring variables are summarised in table 2.

Conclusions

RHF is a common complication of pre-capillary PH and remains the most frequent cause of death in this population. Improving prognosis of these patients will be a great challenge for

Table 2. Main monitored variables

System	Tools	End-points
Right heart failure		
Cardiac output	Echocardiography Right heart catheter $S_{v}O_2$ monitoring	Maintain cardiac output
Systemic pressure	Arterial pressure monitoring	Mean arterial pressure >65–70 mmHg
Heart rate	ECG	Detect and treat arrhythmias
Biomarkers	Serum BNP/pro-BNP dosage	Decreasing level of BNP/pro-BNP
	Serum troponin dosage	Normalisation of troponin level
	Serum lactate dosage	Normalisation of lactate level
End organ failure		
Renal function	Estimated glomerular filtration rate Diuresis	Normalisation of renal function
Liver function	Transaminases/bilirubin dosage	Avoid venous congestion and/or ischaemia
Gut	Feeding tolerance	Avoid food intolerance
Water balance	Weight	Reach the basic weight
	Urine output	Avoid fluid overload
	Natraemia	Avoid hyponatraemia
Others		
Oxygenation	Oxygen supply	$S_{a}O_2$ >90%
Sepsis	Temperature and inflammation monitoring (CRP, PCT)	Detect and treat associated sepsis

$S_{v}O_2$: mixed venous oxygen saturation; BNP: brain natriuretic peptide; CRP: C-reactive protein; PCT: procalcitonin.

the future. The development of PAH-targeted therapies and their use in combination has probably contributed to delay the occurrence of this life-threatening condition in patients with PAH. Active research is ongoing to improve assessment of right ventricular function and to anticipate the risk of this potentially fatal complication in subjects suffering from PAH. A better understanding of physiopathological mechanisms leading to RHF in chronic pre-capillary PH is also necessary to improve its management. At present it remains based on the experience of reference centres with few dedicated clinical trials. Management of RHF in pre-capillary PH is actually based on trigger factor identification, right ventricular afterload improvement, fluid volume optimisation and pharmacological support to improve right ventricular function. At the same time, specific PH therapy according to the aetiology must be considered to optimise the chances of recovery from RHF and to decrease the risk of relapse in the long term. The development during the past decade of ECLS and the optimisation of graft allocation rules in most countries were a first step contributing to improve the outcome of patients with refractory RHF despite optimal medical management.

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Chapter 4

Acute exacerbations of COPD

Alison Patricia Butler[1], Laura-Jane E. Smith[2] and Alexander John Mackay[3]

Exacerbations of COPD cause considerable morbidity and mortality, and are among the commonest causes of medical admissions to hospital. Exacerbations of COPD are triggered predominantly by infection, resulting in increased airway inflammation in association with a deterioration in symptoms and lung function. Current management remains dependent on short-acting bronchodilators, oral corticosteroids and antibiotics, despite limited and often contradictory results of clinical trials for these therapies. Careful oxygen administration is appropriate in the context of hypoxia. Ventilatory support, both noninvasive and invasive, is extremely effective during COPD exacerbations and should be considered and initiated early. Where appropriate, palliative care is also an integral part of management, and rapid initiation of supportive and end-of-life care in such circumstances is essential. Future research is required to identify novel additional treatments in the acute setting, in particular targeting the excess inflammation seen at exacerbation.

COPD is a critically important disease as a leading cause of death worldwide [1]. The World Health Organization estimates that 80 million people worldwide have COPD [2]. Approximately 15 million people in the USA [3] and >3 million people in the UK [4] are estimated to have COPD. COPD is associated with episodic periods of symptom deterioration, termed exacerbations. Exacerbations are among the commonest causes of medical admissions to hospital [5] and are responsible for much of the morbidity [6] and mortality [7] associated with this highly prevalent condition. This chapter discusses the definition, diagnosis and aetiology of COPD exacerbations, and describes acute management, including pharmacotherapy, ventilatory support and the treatment environment, with reference to published studies, meta-analyses and guidelines.

Definition and diagnosis of exacerbations

COPD is a chronic inflammatory condition most commonly resulting from smoking-related damage to the lungs [8]. Noxious agents in cigarette smoke damage the airway epithelium, leading to inflammation and structural changes. The symptomatic hallmarks of the condition are chronic dyspnoea, wheeze, cough and sputum production.

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An exacerbation of COPD is defined as an acute worsening of respiratory symptoms, accompanied by a variable degree of physiological deterioration [9]. The critical study by ANTHONISEN *et al.* [10] defined exacerbations symptomatically, with a particular focus on the symptoms of increased dyspnoea, sputum volume and sputum purulence. However, most pharmaceutical studies have used a healthcare utilisation definition, based on a sustained worsening of the patient's condition from the stable state that requires a change in regular medication [11], which frequently takes the form of unscheduled physician visits, the use of antibiotics or oral steroids at exacerbation, and hospital admission.

A healthcare utilisation definition of exacerbations has significant limitations. Healthcare use in COPD varies depending on access, resulting in a lack of generalisability across different healthcare systems. Most importantly, up to two-thirds of COPD exacerbations are not reported to healthcare professionals and are either self-treated or untreated, and so may not be captured by such definitions. Unreported exacerbations are important events to recognise and quantify. Previous studies have shown that up to two-thirds of all exacerbations are not reported to healthcare professionals for evaluation and treatment [6, 12]. These events impair health-related quality of life [13], and failure to report exacerbations is also associated with an increased risk of emergency hospitalisation [14].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy defines an exacerbation as "an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD" [15]. Regrettably, to date no single biomarker or panel of biomarkers has been found that can reliably diagnose an exacerbation [16]. Furthermore, patient-reported outcomes such as the EXAcerbations of Chronic pulmonary disease Tool (EXACT) have not been capable of reliably detecting exacerbations [17, 18]. Thus, an exacerbation is a clinical diagnosis based on history and examination, and does not rely upon any single investigation, invasive or otherwise.

This definition can be problematic, since the symptoms of COPD exacerbations are nonspecific, and a deterioration in breathlessness and/or sputum production may be caused by alternative diagnoses in patients with COPD other than a COPD exacerbation [19]. Both pneumothoraces and pulmonary embolism, for example, have a higher incidence in the COPD population and can give rise to one or all of the previously described symptoms. Therefore, the diagnosis of COPD requires that other pathologies must simultaneously be ruled out using clinical acumen and appropriate investigations (such as chest radiograph, electrocardiogram and, in some circumstances, CT pulmonary angiogram) if required.

Exacerbation aetiology

Exacerbations are associated with increased systemic and airway inflammation, and may be precipitated by environmental factors. However, the majority of COPD exacerbations are triggered by bacterial and/or respiratory viral infections (figure 1) [20].

Bacteria are isolated from sputum using standard culture techniques in 40–60% of exacerbations [21]. The three most common species isolated in COPD exacerbations are *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Less frequently, *Pseudomonas aeruginosa*, Gram-negative *Enterobacteriaceae*, *Staphylococcus aureus*,

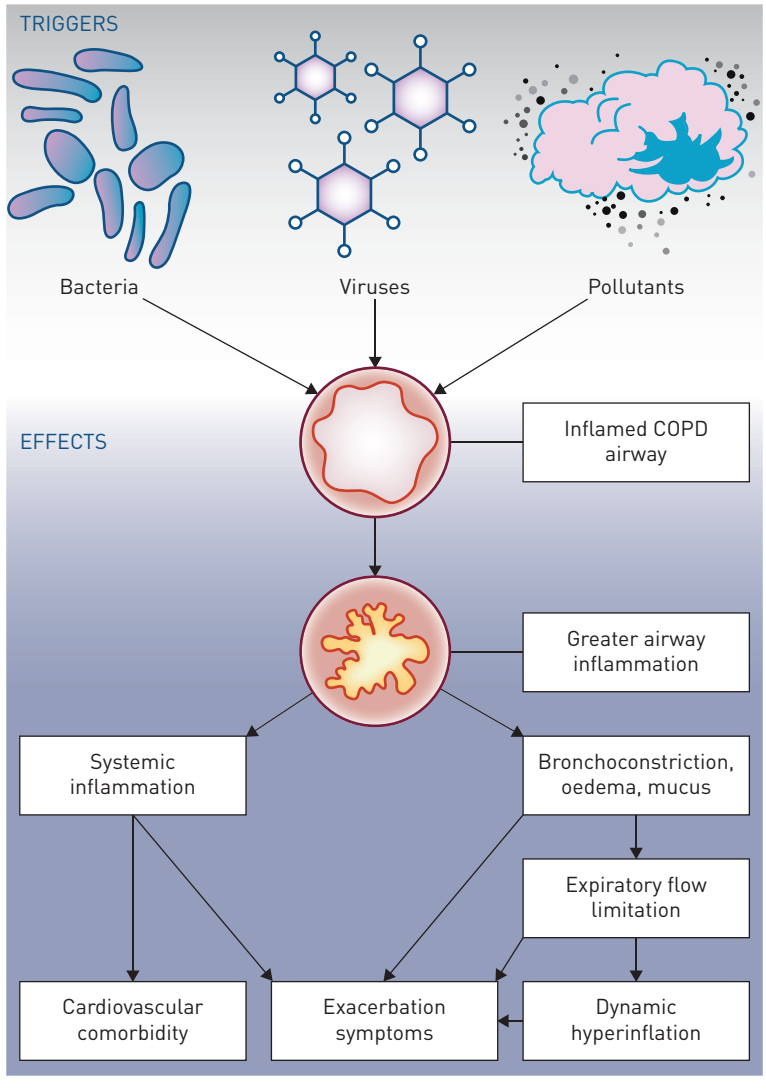

Figure 1. Triggers of COPD exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms. Reproduced from [20] with permission.

Haemophilus parainfluenzae and *Haemophilus haemolyticus* are detected [22–24]. Bacteria are present in the airways of patients with stable COPD when measured using quantitative PCR, and airway bacterial prevalence and load increase during COPD exacerbations when measured using quantitative PCR [25]. Therefore, bacteria are likely to be an important potential aetiological factor in exacerbations.

Respiratory viral infections are detected in up to 60% of exacerbations using PCR techniques, with rhinoviruses being the most common species identified [26, 27]. Experimental rhinovirus infection models also provide evidence of a direct causal relationship between respiratory virus infection and acute exacerbations of COPD [28]. Furthermore, viral and bacterial infections demonstrate a synergistic effect at exacerbation, with exacerbation symptoms, a decline in FEV_1 and inflammation all being more severe in the presence of bacteria and viruses [29].

Original studies of the respiratory tract made the presumption that the healthy human lung was sterile, which we now know to be incorrect. The advent of next-generation sequencing technologies has allowed the investigation of a previously unappreciated, complex microbial community, referred to as the microbiome [30]. It has recently been proposed that exacerbations of COPD may occur due to disorder and dysregulation of the dynamic homoeostasis of the airway microbiome, known as respiratory dysbiosis. In this hypothesis, an inflammatory trigger (such as a viral infection) initiates airway inflammation, which alters the environmental growth conditions of airway microbiota. Altered growth conditions result in a disordered microbiome, which provokes further airway inflammation, leading to a self-amplifying cycle of airway inflammation and respiratory dysbiosis [31]. In such studies conducted during stability, pathogenic *Proteobacteria*, particularly *Haemophilus* spp., are more frequent in COPD patients than in controls [32], and recent work examining the airway microbiome in small numbers of patients at baseline and at exacerbation has shown that the microbiota members that increased at exacerbation were primarily members of the phylum *Proteobacteria*, including nontypical COPD pathogens. Microbiome composition varies depending upon the treatment given [33], and future treatment regimens may seek to target the respiratory microbiome to improve clinical outcomes.

Exacerbation management

Currently, exacerbation therapy is typically administered in a stepwise model (figure 2) [34]. The mainstay of exacerbation therapy is an increase in the dose and frequency of short-acting bronchodilators and systemic corticosteroids. Antibiotics are reserved for exacerbations associated with increasing sputum volume or purulence.

β_2-agonists and anticholinergics

The pathophysiology underpinning COPD exacerbations involves an increase in airway inflammation, leading to bronchoconstriction. Short-acting bronchodilators are therefore one of the primary management options during an exacerbation.

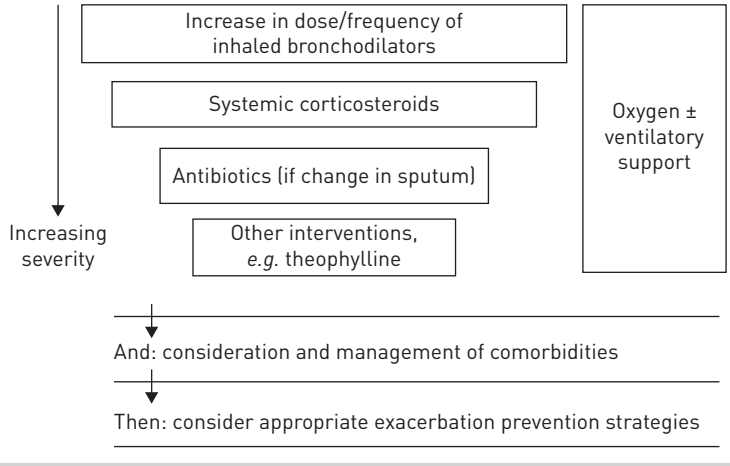
Increase in dose/frequency of inhaled bronchodilators
Systemic corticosteroids
Antibiotics (if change in sputum)
Other interventions, *e.g.* theophylline
Oxygen ± ventilatory support
Increasing severity
And: consideration and management of comorbidities
Then: consider appropriate exacerbation prevention strategies

Figure 2. Stepwise management of COPD exacerbation. Reproduced from [34] with permission.

Both GOLD and the National Institute for Health and Care Excellence (NICE) guidance recommend short-acting inhaled β_2-agonists as the first-line bronchodilator therapy, adding in antimuscarinic agents should this prove insufficient [15, 35]. However, there are few data that provide a comparison of either of these agents with one another, or with placebo. A study has shown similar improvements in FEV1 at 90 min with both drugs, although it did not use newer agents, such as salbutamol, which is in regular use today [36]. The same meta-analysis also concluded that there was no improvement when an anticholinergic was added to a short-acting inhaled β_2-agonist [36]. Both nebulisers and hand-held inhalers can be used to administer inhaled bronchodilators during exacerbations of COPD, and the choice of delivery method should consider the ability of the patient to use the device, the symptom burden and the dose of drug required [35].

An alternative strategy espoused in some centres for the inpatient management of acute COPD exacerbations involves increasing the use of long-acting bronchodilators, in addition to short-acting bronchodilators. Increasing the dose of a patient's own long-acting bronchodilator theoretically has the advantage that inhalation techniques may be checked and optimised at the same time, so that after hospital discharge patients are more experienced at using their own device. Using a long-acting inhaler may also prevent the rapid relapse of symptoms that can occur when short-acting bronchodilators alone are utilised. This approach has not specifically been validated externally, although a recent Cochrane review found no difference between nebulisers *versus* pressurised metered dose inhalers plus a spacer regarding the primary outcomes of FEV1 at 1 h and safety during exacerbations of COPD, although the review was hampered by limited data [37].

In acute exacerbations of asthma, intravenous β_2-agonists have been shown to have a similar efficacy to nebulised ones but with a higher rate of side-effects [38]. No such studies have been identified in COPD, and current guidelines for COPD do not recommend the administration of these agents *via* an intravenous route.

Corticosteroids

COPD exacerbations are inflammatory in nature. The use of corticosteroids to dampen this immune response therefore seems plausible, and multiple studies have found significant short-term benefits of corticosteroids in the treatment of COPD exacerbations. Corticosteroids lead to improvements in FEV1 in the first 3–5 days of treatment [39–41] and in P_{aO_2} in the first 72 h in comparison with placebo [42]. Corticosteroids have also been shown to reduce the length of hospitalisation [41, 42], and a 2014 Cochrane review comparing systemic corticosteroid use with placebo showed that steroids reduced the risk of treatment failure in patients by over one-half compared with placebo [43]. Unfortunately, improvements in lung function are not sustained at 30 days, and treatment of COPD exacerbations with corticosteroids does not improve overall mortality [43]. Nevertheless, guidelines recommend that all patients admitted to hospital with an exacerbation should receive systemic corticosteroid therapy, as should patients in the community with significant breathlessness that interferes with daily living [15, 35].

Controversy exists regarding the optimal dose and duration of treatment for acute exacerbations, often due to the heterogeneity of treatment regimens in different clinical trials. Higher doses (>80 mg) are no more effective than lower doses (30–80 mg) [44], and there is no clear benefit of intravenous therapy over oral preparations. Therefore, most guidelines

recommend 30–40 mg oral prednisolone where an enteral route is available [15, 45]. Short courses (⩽7 days) are equally efficacious with respect to rates of treatment failure, risk of relapse, time to next exacerbation, length of hospitalisation and lung function at the end of treatment, compared with extended courses (>7 days) [45]. Shorter courses of therapy reduce the risk of adverse effects, with tapering of dose not required for most patients. The commonest reported adverse effect of corticosteroid therapy is hyperglycaemia, particularly in patients with pre-existing diabetes mellitus [42]. Therefore, the GOLD strategy advises 5 days of treatment, whereas NICE recommends 7–14 days, without specific guidance on which patients should receive longer or shorter treatment courses. There is little evidence to support the use of inhaled corticosteroids in the management of acute exacerbations of COPD, although nebulised budesonide alone may be an alternative [42].

As discussed in a previous section, exacerbations are triggered mainly by bacteria and respiratory viruses, and result in increased airway and systemic inflammation [16, 46]. Typically, the rise in inflammation seen at exacerbation has been considered predominantly neutrophilic [47–49]. However, more recently there has been considerable interest in eosinophilic inflammation, which had previously been thought to be confined more to asthmatic patients. Bafadhel *et al.* [50] used cluster analysis to identify four distinct biological clusters at exacerbation: bacteria-predominant, virus-predominant, eosinophil-predominant, and one associated with limited changes in the inflammatory profile termed "pauci-inflammatory" (figure 3). In their study, 28% of events were associated with sputum eosinophilia, which can be identified using a peripheral blood eosinophil count of 2%. This threshold had a sensitivity of 90% and a specificity of 60% for identifying a sputum eosinophilia of >3% at exacerbation. Subsequently, it has been proposed that the use of corticosteroids, in the stable state, in the form of inhaled corticosteroid-containing combination therapy [51, 52] and in terms of systemic therapy at exacerbation, might have the greatest benefit in patients with peripheral blood eosinophil levels above this threshold, and that in fact use of corticosteroids in non-eosinophilic exacerbations may impair recovery [53]. However, to date, prospective studies using blood eosinophil profiling are limited, and more research is needed prior to the introduction of biomarker-guided corticosteroid therapy at exacerbation.

Antibiotics

As discussed previously, bacteria are thought to play a significant role in the aetiology of COPD exacerbations, and purulent sputum is a reasonable surrogate of bacterial infection [54]. Most guidelines therefore recommend the administration of antibiotics in events associated with sputum purulence [15, 35].

The seminal study by Anthonisen *et al.* [10] is the foundation for these recommendations. This pivotal study investigated antibiotic use in 173 patients over a period of 3.5 years. It was a randomised, double-blind, crossover study comparing antibiotics with placebo at acute exacerbation, which was defined as increased breathlessness, sputum volume and purulence. The study concluded that antibiotics were associated with better success rates and more rapid peak flow improvement, without being associated with more side-effects [10]. However, the benefits were dependent upon the clinical phenotype of the event. Type 1 exacerbations (those associated with increased sputum volume, sputum purulence and dyspnoea) benefited the most, with resolution of symptoms in 63% of the antibiotic-treated exacerbations and 43% of the placebo group. Patients with type 3 exacerbations (who met just one of the three cardinal symptoms) did not show significant benefit.

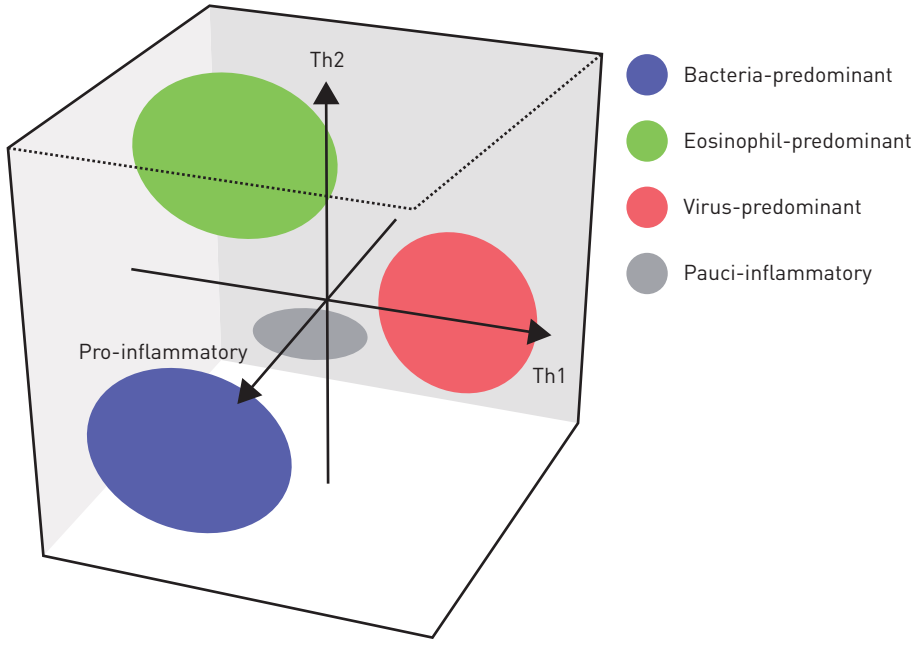

Figure 3. Proportional representation of biological COPD exacerbation clusters in three-dimensional ellipsoids. Cluster 1, shown in blue, is termed "bacteria-predominant", cluster 2 in green is termed "eosinophil-predominant", cluster 3 in red is termed "virus-predominant" and cluster 4 in grey is termed "pauci-inflammatory". Th1: T-helper type 1; Th2: T-helper type 2. Reproduced and modified from [50] with permission.

More recently, antibiotics have been shown to increase the clinical cure rate and prolong the time to next exacerbation in mild to moderate exacerbations (those requiring increased use of bronchodilators, oral antibiotics and/or steroids) [55]. Results for hospitalised patients, however, have been contradictory, and comparisons between studies have been limited by differences in patient selection and antibiotic choice, and by lack of control for interventions that influence outcome, such as the use of systemic corticosteroids and ventilatory support. A recent Cochrane review found that antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients [56]. However, a prospective, randomised, double-blind, placebo-controlled trial of 93 COPD patients at acute exacerbation who required mechanical ventilation found that mortality, duration of mechanical ventilation, length of inpatient stay and treatment failure rates were reduced by the use of oral ofloxacin [57]. This supports the recommendation that antibiotics should be administered in severe exacerbations requiring ventilatory assistance [15].

The addition of antibiotics to oral steroids as part of exacerbation treatment may produce synergistic benefits. Epidemiological research using data from historical cohorts has shown that adding antibiotics to oral corticosteroids as part of the index exacerbation treatment may increase the time to the next exacerbation [58], reduce the risk of future exacerbations [59] and decrease all-cause mortality. However, new data presented to the American Thoracic Society in 2016 from the TEXACOLD trial found that the addition of 7 days of doxycycline treatment to exacerbations treated with 30 mg prednisolone for 10 days did not prolong the time to next exacerbation [60]. Full publication of this study is currently pending, but the efficacy may have been limited by antibiotic choice, with doxycycline having reduced lung penetration compared with other antibiotics, such as amoxicillin and clavulanic acid, and the inclusion of some patients without purulent sputum.

Due to the heterogeneity of results of previous antibiotic trials, potential complications associated with their use and concerns about resistance, biomarkers have been studied in an attempt to target antibiotics to those who would derive most benefit. Procalcitonin (PCT) is a peptide produced in response to endotoxin and other mediators released in bacterial infections. It has been evaluated as a marker of severe bacterial infection, including lower respiratory tract infections and acute exacerbations of COPD [61, 62]. Use of PCT in severe lower respiratory tract infections and COPD exacerbations has been shown to reduce the duration of antibiotic use, with similar rates of adverse outcomes to standard guidelines, suggesting that PCT may have a role in reducing inappropriate antibiotic use during COPD exacerbation [63]. However, PCT is not readily available in most hospitals or community settings. An alternative biomarker, which is readily available, including in point-of-care form, is C-reactive protein. In general practice, C-reactive protein rapid testing has been shown to reduce overprescription of antibiotics without additional adverse outcomes, although this may have been due to sample size limitations [64]. Further research is required in this area.

Oxygen therapy

Hypoxaemia in any circumstance can be life-threatening and should be addressed as a matter of urgency in the acutely unwell patient. However, although this is true for COPD exacerbations, care must be taken over the delivery of oxygen in order to avoid suppression of the patient's respiratory drive and hypercapnia. Oxygen is a prescribed drug, and it is imperative that it is used as a treatment for hypoxia, rather than for breathlessness. As with any intervention in the acutely unwell patient, the patient should be reviewed promptly following initiation to assess the treatment response.

A prevalence study in the UK concluded that 20% of admissions with an acute COPD exacerbation had respiratory acidosis on arterial blood gas (ABG) analysis [65]. This highlights the importance of careful oxygen delivery and early reassessment after initiating therapy. Controlled oxygen delivery, generally achieved *via* a Venturi mask, allows accurate assessment of FIO_2, although it may be poorly tolerated. GOLD guidelines recommend aiming for oxygen saturation of 88–92%, with ABG monitoring 30–60 min after oxygen therapy has been initiated. If the patient remains hypoxaemic and acidotic despite controlled oxygen and best medical therapy, ventilatory assistance should be considered. Figure 4, adapted from the British Thoracic Society (BTS) guidance [66], shows the approach to oxygen delivery in the acutely unwell COPD patient.

Noninvasive ventilation

The mechanics of NIV are discussed in another chapter in this *Monograph* [67], but NIV plays a crucial role in the management of acute COPD exacerbations with hypercapnic respiratory failure. The indications for NIV are shown in table 1; essentially, if a patient remains hypoxic, hypercapnic and acidotic despite best medical therapy, then NIV should rapidly be considered. NIV is an extremely effective treatment for hypercapnic respiratory failure in the context of COPD exacerbations, reducing endotracheal intubation rate, treatment failure and short-term mortality, as well as improving acidosis in the first few hours of treatment [69].

Despite this, NIV is not an appropriate option for all patients, and the contraindications shown in table 1 should be considered. Severe respiratory acidosis (pH <7.25) is often considered a relative contraindication, as these patients have poorer outcomes on NIV [70].

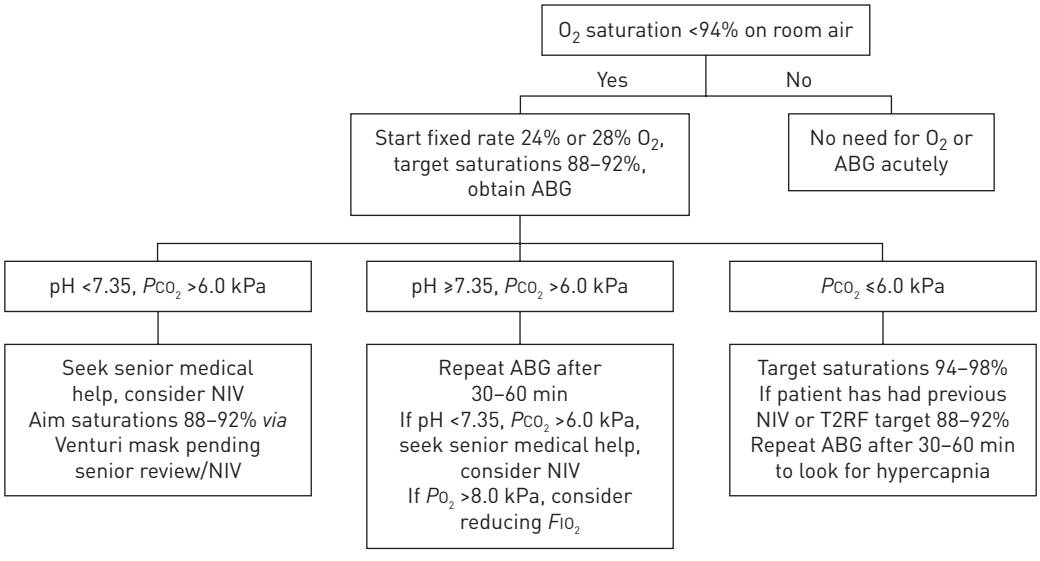
O_2 saturation <94% on room air
Yes
No
Start fixed rate 24% or 28% O_2, target saturations 88–92%, obtain ABG
No need for O_2 or ABG acutely
pH <7.35, P_{CO_2} >6.0 kPa
pH ≥7.35, P_{CO_2} >6.0 kPa
P_{CO_2} ≤6.0 kPa
Seek senior medical help, consider NIV Aim saturations 88–92% *via* Venturi mask pending senior review/NIV
Repeat ABG after 30–60 min If pH <7.35, P_{CO_2} >6.0 kPa, seek senior medical help, consider NIV If P_{O_2} >8.0 kPa, consider reducing F_{IO_2}
Target saturations 94–98% If patient has had previous NIV or T2RF target 88–92% Repeat ABG after 30–60 min to look for hypercapnia

Figure 4. Oxygenation in the acutely unwell COPD patient. ABG: arterial blood gas; P_{CO_2}: partial pressure of carbon dioxide; P_{O_2}: partial pressure of oxygen; T2RF: type 2 respiratory failure. From the British Thoracic Society guidelines for emergency oxygen use in adult patients [66].

Prompt invasive ventilation is more successful in these patients where appropriate. Importantly, a ceiling of care should be established prior to initiation of NIV. By definition, respiratory acidosis at the time of presentation makes an exacerbation "severe", and many of these patients have significant underlying COPD, as well as multiple comorbidities. Should NIV fail, there is a cohort of patients for whom endotracheal intubation and admission to the ICU may not be appropriate. This should be confirmed prior to commencement of NIV, preferably in discussion with the patient.

Once NIV is initiated, ABG monitoring is required to ensure resolution of acidosis and improvement of gas exchange. BTS guidelines advise that the time on NIV should be

Table 1. Indications and contraindications for NIV

Indications for NIV
pH <7.35, P_{CO_2} >6.5 kPa, respiratory rate >23 breaths·min^{-1}
If persisting after bronchodilators and controlled oxygen therapy
Relative contraindications[#]
pH <7.15 (or pH <7.25 and additional adverse features)
Glasgow Coma Score <8
Confusion/agitation
Cognitive impairment (warrants enhanced observation)
Absolute contraindications
Severe facial deformity
Facial burns
Fixed upper airway obstruction

P_{CO_2}: partial pressure of carbon dioxide. [#]: for patients with the relative contraindications listed, treatment with NIV should be carried out in an appropriate area with ready access to staff who can perform safe endotracheal intubation if needed. From the British Thoracic Society/Intensive Care Society guidelines for ventilatory management of acute hypercapnic respiratory failure [68].

maximised in the first 24 h, depending on patient tolerance and/or complications. Thereafter, NIV use during the day can be tapered over the following 2–3 days, depending on the partial pressure of carbon dioxide (P_{CO_2}) levels measured while self-ventilating, before being discontinued overnight. NIV can be discontinued when there has been normalisation of pH and P_{CO_2} and a general improvement in the patient's condition [68].

Invasive ventilation

The indications for mechanical ventilation include failure of NIV and imminent respiratory arrest (table 2). In practice, not all patients are candidates for invasive ventilation, and, as with NIV, an early conversation about treatment escalation is imperative. In end-stage COPD, factors such as comorbidities, frailty and the patient's wishes should all be taken into account prior to making a decision. The main complications associated with mechanical ventilation are ventilator-associated pneumonia, barotrauma and failure to wean [15]. If mechanical ventilation is not appropriate and NIV has failed or the patient is not suitable, early involvement of palliative care should be considered. However, there is evidence to suggest that acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes [71]. If the patient fits the criteria shown in table 2 and would be a candidate for mechanical ventilation, referral should be made early, particularly if NIV is unlikely to be successful or is not improving gas exchange.

Palliative care

Many hospitalised patients have palliative care needs, and such needs may extend for years in chronic diseases such as COPD [72]. It is unclear how best to identify these patients [73–76], and it is challenging to address the social and psychological needs of patients and carers and create a holistic and calm environment in the acute setting [77]. In addition, an acute exacerbation of COPD may be a terminal event, and breathlessness and respiratory failure may be the end stage of a slow decline, mislabelled as an acute exacerbation on initial assessment. A particular challenge for those at the front door is to identify those patients who will benefit from and who wish to receive NIV and intubation, and to initiate such treatments rapidly, but also to identify those for whom such treatments are likely to be unsuccessful and may prolong death. For these patients, rapid initiation of supportive and end-of-life care is essential. Risk scores may facilitate such decision making [78], but at the core must be exploration of patient preferences and advance care planning [79].

Patients with advanced COPD have similar treatment preferences to patients with lung cancer [80] but are more likely to undergo invasive interventions at the end of life [81]. This

Table 2. Indications for invasive ventilation

Imminent respiratory arrest
Severe respiratory distress
Failure of or contraindications to NIV
Persisting pH <7.15 or deterioration in pH despite NIV
Depressed consciousness (Glasgow Coma Score <8)

From the British Thoracic Society/Intensive Care Society guidelines for ventilatory management of acute hypercapnic respiratory failure [68].

is partly due to the fact that they are less likely to complete advanced care planning [79]. Physicians find it challenging to know when is the right time to discuss intubation, ventilation and ceilings of care with patients, and these conversations therefore often occur at a time of crisis [82, 83]. Patients may be "invisible" until they have an exacerbation, as traditional models of care for COPD are reactive and fragmented. Models of care that bridge primary and secondary care and that integrate palliative care alongside disease-focused care are needed since, in such models, advance care planning is improved [84, 85].

Hospital may be the preferred place of care for a greater number of patients with respiratory disease than other conditions, since breathlessness is frightening. It is essential, therefore, to ensure that hospice principles and practices are implemented in hospitals. A good death is absolutely possible in the acute setting but is too often hindered by delays in diagnosis of dying, delays in decision making, lack of confidence in the use of palliative medications, and a default of systems and teams towards investigation and intervention [86–89].

Other interventions

Mucolytics

The role of mucolytics such as carbocisteine is unclear in COPD management. A 2010 Cochrane review suggested that long-term use reduces the frequency of exacerbations and the number of disability days per year [90]. However, their use does not appear to result in an improvement in lung function or quality of life. There is some suggestion that patients not taking inhaled corticosteroids may receive a bigger benefit than those who are, and that patients with very viscous sputum may benefit the most [90]. However, GOLD guidelines do not recommend the use of mucolytics for long-term management at present, and their role in the acute setting has not been established [15].

Methylxanthines

The use of theophylline in the management of COPD has been contentious, with conflicting evidence. It is not currently recommended as a first-line therapy in either acute or chronic management. A prospective double-blind RCT of 80 patients with non-acidotic COPD exacerbations showed a small but statistically significant improvement in P_{aO_2} with intravenous theophylline compared with placebo [91]. However, this did not affect clinical outcome, and patients were found to complain of nausea more commonly. The rate of palpitations and headaches was equal in the placebo *versus* the treatment group. GOLD guidelines recommend that intravenous methylxanthines be used if nebulised β_2-agonists and anticholinergics have failed [15].

Novel anti-inflammatory agents

Treatment failure with the standard of care is 27% at 30 days and rises to 37% at 90 days [43, 92]. Persistently elevated inflammation during exacerbations is associated with clinical nonrecovery and recurrence [93]. Thus, new therapies for the management of acute exacerbations are urgently needed, in particular specifically targeting the increased inflammation seen at exacerbation. Unfortunately, to date attempts to use alternative agents to treat exacerbations have been unsuccessful. As described in previous sections, exacerbations are inflammatory events, and are associated with increased sputum concentrations of tumour necrosis factor (TNF)-α. TNF-α upregulates adhesion molecules, facilitates migration of

leukocytes into the bronchial mucosa during an acute exacerbation of COPD, and stimulates neutrophil degranulation and superoxide production [94].

Etanercept binds to soluble TNF and blocks the interaction of TNF with cell-surface TNF receptors. Therefore, the drug competitively inhibits TNF binding to cell-surface TNF2 receptors, rendering TNF biologically inactive [95]. Observational data suggested that the use of etanercept in patients with both rheumatoid arthritis and COPD reduced hospitalisation risk [96]. Subsequently, AARON *et al.* [97] conducted an RCT to establish whether etanercept improved lung function and decreased treatment failure rates compared with corticosteroids. Both groups received oral antibiotics and bronchodilators as part of standard therapy. Unfortunately, etanercept failed to demonstrate any improved clinical efficacy compared with standard treatment with prednisone with respect to a change in FEV_1 from baseline. Furthermore, the nonsignificant differences observed in the trial tended to favour the prednisolone-treated group, with the relative risk of 90-day treatment failure being greater (by 25%) in those randomised to etanercept.

Alternative anti-inflammatory agents include roflumilast, a phosphodiesterase 4 inhibitor designed to target both the systemic and pulmonary inflammation associated with COPD. COPD exacerbations are associated with increased neutrophilic inflammation [48], and roflumilast demonstrates broad anti-inflammatory activities and has been shown to reduce neutrophilic airway inflammation in COPD patients [98], improve lung function and reduce exacerbations in stable COPD patients [99–101]. Results from a trial assessing the efficacy of roflumilast as an additional therapy at acute exacerbation will report shortly (ClinicalTrials.gov, trial number NCT01473758).

Early inpatient respiratory rehabilitation during an exacerbation

Historically, small-scale trials of exercise-based therapy during acute exacerbation of COPD suggested that such approaches are feasible and may be effective [102–104]. More recently, however, a large prospective RCT tested the efficacy of a 6-week intervention, started within 48 h of admission for an exacerbation of chronic respiratory disease (>80% of patients had a primary diagnosis of COPD). The intervention comprised prescribed, progressive aerobic, resistance and neuromuscular electrical stimulation training. Patients also received a self-management and education package. The results showed no significant effect of early pulmonary rehabilitation on readmission rates in the year after initial admission compared with usual care. An increase in mortality was seen in the intervention group at 1 year but not during the intervention period or at 6 months. Physical performance and health status recovered after discharge in both groups, with no significant difference between the groups at 1 year. Consequently, the authors concluded that, beyond current standard physiotherapy practice, progressive exercise rehabilitation should not be started during the early stages of the acute illness [105].

Self-management

Patient education is vital to improve the management of COPD exacerbations. Rapid recognition of exacerbation symptoms and earlier treatment improves recovery and reduces the risk of hospitalisation [14]. Self-management plans and programmes enable patients to respond appropriately to the first signs of an exacerbation. Patients at high risk of exacerbations are frequently provided with a course of "rescue" antibiotics and corticosteroids, and are instructed to commence oral corticosteroid therapy if their increased

dyspnoea interferes with activities of daily living. Antibiotics should be started in response to increased sputum volume and/or purulence, and bronchodilator therapy should be increased to control symptoms [38]. Depending on patient confidence and support networks, treatment can be initiated either independently or after seeking advice from a healthcare professional. Such interventions reduce admission rates [106, 107]; however, not all patients are suitable for these strategies. Anxiety and depression is common in COPD, and patients are frequently elderly and may have cognitive impairment, limiting their ability to self-manage, particularly when acutely unwell. Further research is required in this area, with a focus on identification and management of patients at high risk of hospital admission.

Admission to hospital

Mild COPD exacerbations can be managed safely in the community. However, deciding who fulfils the criteria of a "mild" exacerbation can be difficult in practice. The NICE COPD guidelines from 2010 specifically address the issue of admission to hospital [35]. Table 3 is adapted from these guidelines, and indicates that hypoxic, acidotic or confused patients warrant automatic admission, and that careful consideration should be given to patients with severe underlying disease, such as those receiving long-term oxygen therapy [35]. Patients with a good baseline level of function who are only mildly breathless can be managed at home. Particular care must be taken over discharging vulnerable, frail patients. In such circumstances, even if symptoms appear mild, admission may be warranted if patients are unable to cope at home and/or live alone without assistance.

Prognosis

Due the heterogeneity of symptoms that can worsen during an exacerbation of COPD, standardised instruments have been developed to evaluate the severity of exacerbations.

Table 3. Factors to consider when deciding where to treat patients

Factor	Home	Hospital
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity	No	Yes
$Sa0_2$ <90%	No	Yes
Changes on chest radiograph	No	Yes
Arterial pH level	⩾7.35	<7.35
$P0_2$	⩾7 kPa	<7 kPa

LTOT: long-term oxygen therapy; $Sa0_2$: arterial oxygen saturation; $P0_2$: partial pressure of oxygen. From the National Institute for Health and Care Excellence guidelines for the management of COPD exacerbations [35].

Two such patient-reported outcome tools, the COPD Assessment Test (CAT) and EXACT, have recently been shown to be effective instruments to monitor COPD exacerbation severity and recovery in outpatients [17, 108]. Furthermore, in hospitalised patients, exacerbation CAT scores relate to length of stay [109], and patients with higher CAT score increases during the initial days of hospitalisation and with higher area-under-the-curve CAT scores for the first 5 days of exacerbation may be more likely to require hospitalisation for a recurrent exacerbation [110].

More-objective measures may also be utilised to determine exacerbation prognosis. The Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) scoring system uses the following parameters, which are routinely available when patients attend hospital: extended Medical Research Council dyspnoea score, eosinopenia ($<0.05\times10^9$ eosinophils·L^{-1}), consolidation on chest radiograph, acidaemia (arterial pH <7.30) and atrial fibrillation. The scoring system predicts mortality and may identify both low-risk patients (DECAF score 0–1) who may be suitable for Hospital at Home or early supported discharge schemes, as well as high-risk patients (DECAF score 3–6) for escalation planning or appropriate early palliation [77]. More recently, smaller quadriceps muscle size, as measured by ultrasound in the acute care setting, has been shown to be an independent risk factor for unscheduled readmission or death in patients hospitalised with an exacerbation of chronic respiratory disease [111], although at the present time this remains predominantly a research tool and is not commonly available in clinical practice.

Conclusion

Exacerbations are critical events in COPD. Current management remains dependent on short-acting bronchodilators, oral corticosteroids and antibiotics, despite limited and often contradictory results of clinical trials for these therapies. Careful oxygen administration is appropriate in the context of hypoxia. Ventilatory support, both noninvasive and invasive, is extremely effective during COPD exacerbations, and should be considered and initiated early. Where appropriate, palliative care is also an integral part of management, and rapid initiation of supportive and end-of-life care in such circumstances is essential. Future research is required to identify novel additional treatments in the acute setting, in particular targeting the excess inflammation seen at exacerbation.

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Chapter 5

Acute exacerbations of asthma

Nirav R. Bhakta[1] and Stephen C. Lazarus[1,2]

Acute severe asthma exacerbations are a significant cause of morbidity and mortality. A high proportion of severe exacerbations and deaths result from undertreatment. Risk factors for fatal asthma have been identified and should guide treatment. The time course for recovery from an exacerbation mirrors that for onset of signs and symptoms. Thus, early intervention is critical. Patients must be taught to adjust maintenance treatment to prevent an exacerbation, as well as how and when to initiate treatment. Home treatment consists of aerosolised short-acting β_2-agonists, and systemic corticosteroids. If symptoms persist after ~1 h, the patient should seek urgent medical attention, where the emphasis should be on briefly confirming the diagnosis and severity, while initiating therapy with inhaled bronchodilators and systemic corticosteroids and oxygen, titrated to SpO_2 93–95%. The decision to admit or discharge should be made within 1–3 h. For patients who progress to respiratory failure, there are unique management issues related to noninvasive positive-pressure ventilation, intubation, ventilator settings and medications.

Asthma is a common disease, and acute severe exacerbations are a significant cause of morbidity and mortality throughout the world. A high proportion of severe exacerbations and deaths result from undertreatment. Risk factors for fatal asthma include previous severe exacerbations, hospitalisation in the past year, three or more emergency department (ED) visits in the past year, recent use of oral corticosteroids, use of one or more canisters of short-acting β_2-agonist (SABA) per month, a history of poor adherence, medical comorbidities and illicit drug use. In addition, up to 50% of fatal asthma occurs in patients thought to have had mild or moderate asthma [1–3].

The time course for recovery from an exacerbation mirrors that for onset of signs and symptoms. Thus, early intervention is critical. Education to teach patients how to adjust maintenance treatment to prevent exacerbations, how to recognise an exacerbation, and how and when to initiate treatment has been shown to improve outcomes [4, 5]. Objective measurement of lung function (*e.g.* peak expiratory flow (PEF) or FEV1) can be helpful.

Treatment at home consists of aerosolised SABAs with assessment of response at ~1 h. At this point, a decision should be made to continue home treatment or to seek urgent medical attention. In the urgent care setting, the emphasis should be on briefly confirming the diagnosis and severity, while initiating therapy with inhaled bronchodilators and

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systemic corticosteroids and oxygen, titrated to S_{pO_2} 93–95%. Patients should be reassessed after ~1–3 h of treatment, and the decision to admit or discharge should be made then. Patients who are admitted to hospital generally have not only bronchoconstriction but also significant airway inflammation, and often mucus hypersecretion. These resolve slowly and require continued aggressive treatment. These patients can relapse rapidly if treatment is stepped down too early, and can progress to respiratory failure as well. The approach to respiratory failure in the asthmatic patient requires specialised knowledge of the pathophysiology of asthma.

Epidemiology

Asthma is a common diagnosis throughout the world, especially in developed countries, with a global prevalence of 7–10% [6]. Prevalence is increasing in many countries, especially among children. In the USA, the prevalence of asthma increased from 3.1% in 1980 to 5.5% in 1996, 7.3% in 2001 and 8.4% in 2010 [7]. The rate of increase was greater in black persons compared with white, and in Hispanic persons compared with non-Hispanic. In Europe, approximately 30 million children and adults <45 years of age have asthma, and the prevalence increased significantly in the latter half of the 20th century before levelling off [8]. Because of its high prevalence, asthma accounts for a high proportion of urgent care and ED and hospital visits (figure 1). In 2009 in the USA, asthma accounted for approximately 2 million ED visits, 500 000 hospitalisations and 3388 deaths [7]. In the European Union, asthma accounts for only a small percentage of deaths [8], but a recent UK study identified major preventable factors in two-thirds of asthma deaths [10]. Most factors related to insufficient prescribing of corticosteroid preventer medications, failure to monitor asthma control and failure to refer patients to an asthma specialist. In many instances, patients with fatal asthma were thought to have mild asthma and thus were not prepared to recognise danger signals and the need for help. Easily obtainable information on Asthma Control Questionnaire scores, current smoking, chronic sinusitis, previous hospitalisations for asthma and one or more severe exacerbations in the previous year identifies patients who are prone to asthma exacerbations [11]. Adding spirometry improves the accuracy of this predictive model. In several countries, targeted asthma programmes have been shown to reduce asthma costs, as well as morbidity and mortality [12, 13].

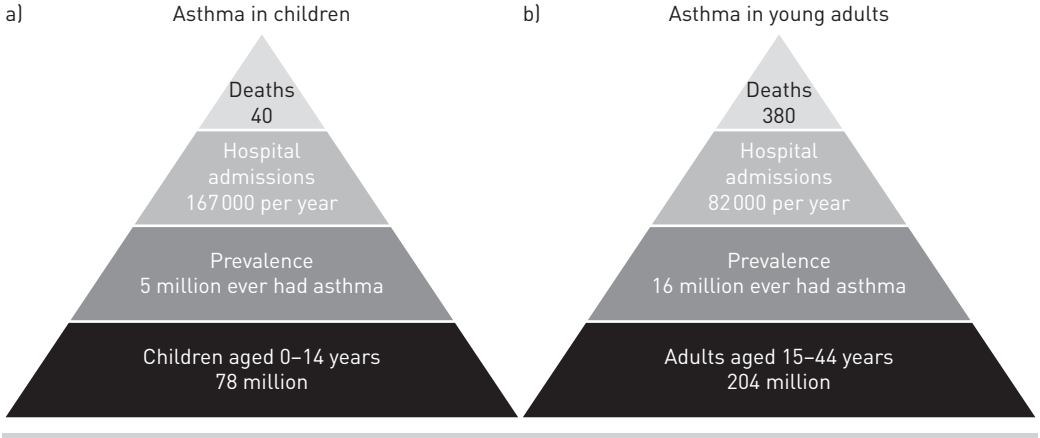

Figure 1. The burden of asthma in a) children and b) young adults, around 2010, in the 28 countries of the European Union. Reproduced from [9] with permission.

Prevention of asthma exacerbations

Early adjustment of maintenance regimens can "rescue" patients with worsening asthma control before they develop an exacerbation. The Global Initiative for Asthma (GINA) suggests that action plans recommend an early increase in inhaled corticosteroid (ICS) dose [4], or that patients follow a single maintenance and reliever therapy ("SMART") regimen, using a single inhaler that contains both an ICS and a rapid-onset long-acting β_2-agonist [5]. More important than the specific regimen is that patients are educated to recognise and treat poor asthma control before it exacerbates.

Home management

Early recognition of an impending exacerbation and early institution of treatment are key to improving outcomes (figure 2). In contrast, delayed intervention is associated with worse prognosis. A review of fatal asthma in the UK found that 45% of patients had not sought help, and that 70% and 83% of children and adolescents, respectively, died before they reached hospital [10]. Only 23% of patients who died had received a personalised asthma action plan. Education that provides patients with the information necessary to assess their asthma control, and guidelines for when to seek help, can reduce morbidity and mortality. Similarly, providers should ensure that patients, especially those with prior exacerbations, are

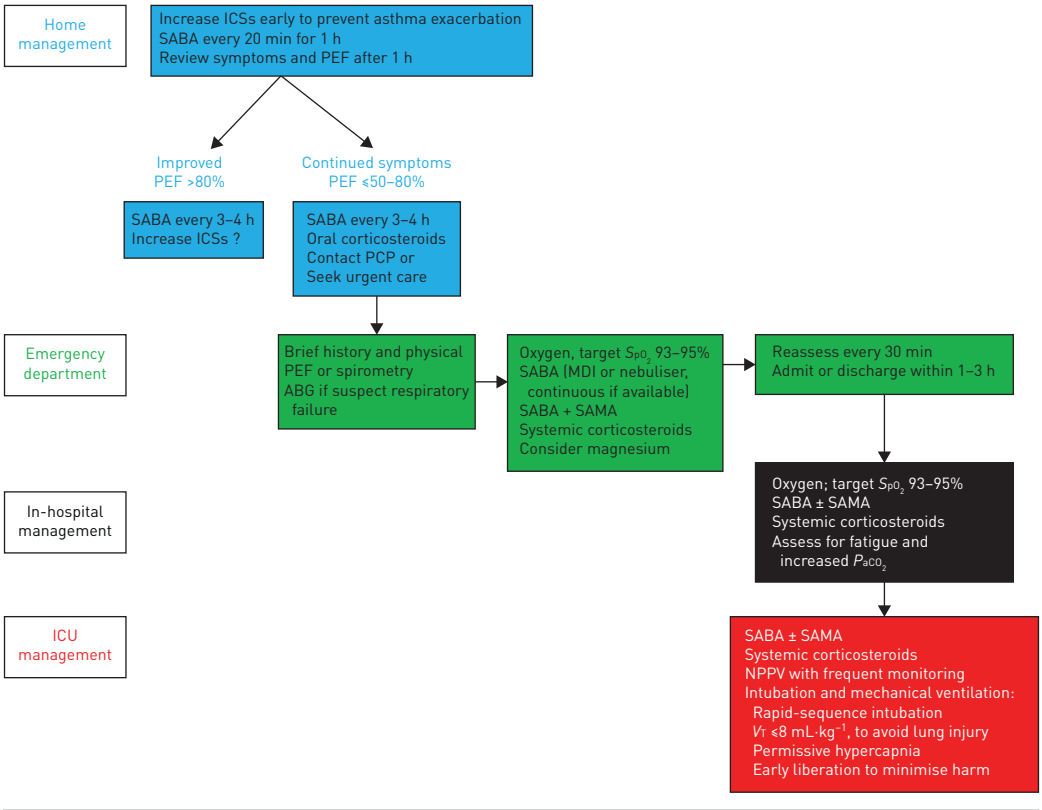

Figure 2. Management of asthma exacerbations. ICS: inhaled corticosteroid; SABA: short-acting β_2-agonist; PEF: peak expiratory flow; PCP: primary care provider; ABG: arterial blood gas; MDI: metered-dose inhaler; SAMA: short-acting muscarinic antagonist; NPPV: noninvasive positive-pressure ventilation; V_T: tidal volume.

prescribed and are taking the appropriate asthma medications. In the previously mentioned UK study, 39% of patients who died used SABAs excessively ($\geqslant$12 canisters·year^{-1}) and 4% had used >50 canisters·year^{-1} [10]. In addition, a significant proportion of patients who died were not taking ICSs regularly.

Initial treatment at home

Most patients with asthma, and certainly those with prior severe or life-threatening asthma, should be taught self-management of exacerbations [14, 15]. A written personalised action plan can facilitate intervention.

Treatment is usually initiated with inhaled SABAs, with two to four puffs *via* a metered-dose inhaler (MDI) with a spacer, repeated every 20 min for 1 h. If the exacerbation was triggered by an environmental exposure, every effort should be made to separate the patient from the offending stimulus. If, after 1 h, symptoms have resolved and PEF has improved significantly (to >80% of personal best), then the patient may continue self-management with an inhaled SABA every 3–4 h for 24–48 h. The patient should contact his/her healthcare provider, who may choose to add or increase the dose of ICSs, or to initiate oral corticosteroids.

If, after 1 h of treatment, symptoms continue and/or the PEF is at 50–80% of the personal best range, the patient should start oral corticosteroids (if included in their personal asthma action plan) and contact his/her provider for further instructions. Use of SABAs should be continued every 3–4 h.

Patients with a PEF of <50–60% of predicted, with very severe or increasing symptoms, or with patient risk factors for fatal asthma should seek urgent medical attention.

Management in urgent care or the ED

Patients should be evaluated rapidly to confirm the diagnosis of asthma exacerbation, assess the severity of the event and determine the need for urgent intervention [14, 15]. A brief history and physical examination should focus on conditions such as pneumothorax, altered mental status or a quiet chest that would necessitate different treatment. Risk factors for fatal asthma should be reviewed (table 1). This assessment should be performed simultaneously with initiation of treatment. Few laboratory tests should be routine, and none should delay the initiation of therapy. If respiratory failure seems imminent, $P_{a}CO_2$ should be monitored; suspicion of pneumonia may warrant a chest radiograph or complete blood count; concern for myocardial infarction, arrhythmia or heart failure may lead to an electrocardiogram or echocardiogram.

Every patient should be treated simultaneously with oxygen, an inhaled SABA and systemic corticosteroids. Oxygen should be titrated to $S_{p}O_2$ 93–95%, as higher levels have been associated with worse physiological outcomes [16–18].

β_2-Adrenergic agonists

Inhaled SABAs are the most effective bronchodilators and should be administered as soon as possible after presentation to the ED. In patients who are able to master the technique,

Table 1. Risk factors for fatal asthma

Prior near-fatal exacerbation
Hospitalisation or emergency department visit in past year
Recent use of systemic corticosteroids
SABA use >12 canisters·year^{-1}
Psychiatric disorder
Use of illicit drugs
Comorbid medical conditions
History of poor adherence to medications or action plan
"Poor perceiver"
Food allergy
Not currently using inhaled corticosteroids

SABA: short-acting β_2-agonist. Information from [15].

the use of an MDI combined with a valved holding chamber or spacer is as effective as the use of a pressurised nebuliser [19–21]. Unfortunately, many patients with severe exacerbations are too dyspnoeic to use an MDI effectively. The choice between continuous *versus* intermittent nebulisation is somewhat controversial, as individual trials as well as systematic reviews have produced conflicting results. Although early meta-analyses suggested either no difference between intermittent and continuous nebulisation in the ED [22] or an advantage with as-needed *versus* scheduled intermittent therapy in patients who were already hospitalised [23], the latest Cochrane review of eight acceptable trials suggested that lung function improved more and there were fewer hospital admissions in patients treated in the ED with continuous nebulisation, especially those patients with severe asthma [24]. Based on these reports, the latest GINA guidelines suggest the use of continuous nebulised salbutamol (albuterol) initially in the ED, followed by intermittent therapy for patients who are hospitalised [15].

Salbutamol is the most widely used bronchodilator in the world, and is listed by the World Health Organization as one of the essential medications needed in a basic healthcare system [25]. It is available as a racemic mixture of the R- and S-enantiomers. The latter are thought to be responsible for adverse effects (*e.g.* tachycardia, palpitations), which led to the development of levosalbutamol (levalbuterol), the R-enantiomer. Although effective at approximately half the dose of racemic salbutamol, it has not been convincingly demonstrated to offer a clinical advantage over the racemic preparation in the ED [26, 27]. Oral administration of β_2-agonists is not recommended, as the onset of action is slower and systemic side-effects are greater, compared with inhalation. Similarly, a Cochrane analysis found insufficient evidence to recommend the use of intravenous β_2-agonists in acute asthma [28]. Some authors suggest the use of the nonselective adrenergic agonist epinephrine in patients with severe asthma that is refractory to standard therapy [29]. Although possibly acting to decrease airway mucosal oedema, there is not sufficient evidence to support this approach. Finally, the long-acting β_2-agonist formoterol has a relatively rapid onset of action, and a systematic review and meta-analysis of nine RCTs found no significant difference compared with SABAs for lung function, adverse effects and hospitalisations [30]. However, the authors identified the quality of the studies analysed as low, and as a result, most experts think further studies are needed before formoterol can be recommended as treatment for asthma exacerbations.

Muscarinic antagonists

Antimuscarinic (anticholinergic) drugs can be effective bronchodilators, although their onset of action is less rapid than that of salbutamol. For this reason, aerosolised ipratropium should not be used as a monotherapy in the ED. Results of studies of the combination of a SABA and ipratropium have not been consistent but suggest that the combination results in greater improvement in lung function and approximately 25% fewer hospitalisations than SABA use alone [31, 32]. This benefit may not carry over once patients are hospitalised [33]. Long-acting muscarinic antagonists are not appropriate for use in the ED or ICU.

Inhaled corticosteroids

In patients with mild-to-moderate exacerbations or loss of asthma control, increasing the dose of ICSs may be useful, although this is best implemented when signs and symptoms increase, before an exacerbation occurs. Doubling the dose of ICSs may not be sufficient [34], but quadrupling the dose of ICSs has been reported to reduce the need for oral corticosteroids [35, 36]. A recent Cochrane review concluded that, in patients who were not already taking ICSs, high-dose ICSs given early in the ED reduced hospital admissions [37]. Despite this, guidelines recommend that nearly all patients treated in the ED receive systemic corticosteroids [14, 15].

Systemic corticosteroids

Unless symptoms and lung function reverse rapidly and almost completely in response to initial treatment with an inhaled β_2-agonist, systemic corticosteroids are warranted, and guidelines recommend administration within the first hour in the ED [14, 15]. Such treatment results in a more rapid improvement in FEV_1 and PEF, fewer hospitalisations and a lower rate of relapse after discharge [38–42]. In patients who are unable to swallow because of altered mental status or respiratory status, or who have nausea, vomiting or suspected malabsorption, corticosteroids may be given intravenously; in most patients, oral administration is preferred. Numerous studies have shown that oral administration is as effective at improving lung function and reducing hospital length of stay as intravenous administration.

Although the optimal dose of systemic corticosteroids is not known, most studies have suggested that high doses are not necessary [15]. When administered orally, prednisone or prednisolone is absorbed rapidly and has high bioavailability. GINA guidelines recommend the equivalent of 50 mg prednisolone given as a single morning dose [15]; the Expert Panel Report 3 (EPR-3) suggests 40–80 $mg \cdot day^{-1}$ in one or two divided doses [14]. Treatment for 5–7 days is as effective as 10–14-day regimens [43, 44], and tapering is not necessary if the treatment course is 7–10 days, especially if patients are taking ICSs concomitantly.

Magnesium

Case reports and uncontrolled studies going back more than 75 years have described the beneficial effects of intravenous magnesium in asthmatic patients refractory to standard treatment [45, 46]. In 1989, Skobeloff *et al.* [47] conducted a double-blind placebo-controlled trial of intravenous magnesium *versus* placebo in 38 patients with acute exacerbations of

asthma who failed to respond to ED treatment with a β_2-agonist. They found greater increases in PEF and fewer hospitalisations in the group who received a single infusion of 1.2 g of magnesium sulphate. Since that time, use of magnesium in the ED has become common for patients with severe exacerbations refractory to initial treatment. A 2009 survey of EDs in the UK found that 93% used magnesium in this situation [48]. Clinical trials, however, have provided conflicting results and do not support this widespread usage. Several have shown benefit in patients who presented with very low FEV1 and in those with persistent hypoxaemia [49–51], but a more recent large RCT found no additional benefit when magnesium was administered intravenously or by nebulisation [52]. However, this latter trial excluded participants with severe asthma, which is the group shown previously to be most responsive. Because it is generally thought to be safe, use of magnesium can be considered in severe exacerbations that have not responded to initial interventions.

Leukotriene modifiers

Data from early in the development of leukotriene modifier drugs suggested that they might be useful for treatment of acute asthma exacerbations [53, 54]. Subsequent studies of intravenous or oral montelukast found a transiently higher FEV1 but no reduction in rate of hospitalisation or length of stay after admission [55, 56]. Finally, a Cochrane review of eight trials that included 1470 adults and 470 children found no significant difference in hospital admission rates and found inconsistent effects on lung function [57]. Thus, leukotriene modifiers should not be used routinely for treatment of acute exacerbations of asthma, and additional studies are needed to determine if they have any role in this setting.

Aminophylline

Prior to the development of effective, inhaled forms of selective β_2-agonists, methylxanthines were used routinely for the emergency treatment of asthma. Although they are effective bronchodilators, their narrow therapeutic margin makes them far less attractive than β_2-agonists as a monotherapy. Several Cochrane reviews have concluded that intravenous aminophylline combined with standard care adds adverse effects but no benefit [*e.g.* 58].

Treatments that are not recommended

Treatments that are not recommended or that have no evidence to support their use in routine asthma exacerbations are listed in table 2. Although exacerbations are often triggered by respiratory infections, these are usually viral, and the routine use of antibiotics to treat exacerbations is not supported by evidence. Antibiotics may be warranted if fever, purulent sputum, or sinusitis or pneumonia is present. Similarly, sedative hypnotics should not be used because of the potential for respiratory depression and increased morbidity and mortality [59, 60]. Heliox, a mixture of helium and oxygen that is less dense than air, has been shown to increase airflow in some studies, but a systematic analysis did not demonstrate an impact on hospitalisation or other clinical outcomes [61].

Assessment of response in the ED

Treatment for acute asthma should not be open-ended, and most experts recommend that a decision to discharge to home or admit to hospital should be made within 1–3 h [14, 15]. Specific criteria and guidelines are provided in the GINA and EPR-3 documents [14, 15].

Table 2. Treatments without evidence to support their routine use in asthma exacerbations

Treatments without evidence
Magnesium (inhaled or intravenous) or leukotriene modifiers
Ketamine or inhaled anaesthetics for bronchodilation
Bronchoscopy to remove mucus
Mucolytics (*N*-acetylcysteine, DNase)
Treatments that are not recommended
Intravenous salbutamol (albuterol)
Subcutaneous or intravenous terbutaline, epinephrine and aminophylline
Heliox
Antibiotics in the absence of suspected infection

Of note, assessment of asthma severity after 1 h of treatment in the ED is a better predictor of the need for hospitalisation than assessment at initial presentation [62].

Treatment in the hospital

Patients whose symptoms and lung function have not improved after initial treatment in the ED should be admitted to hospital for further aggressive treatment and close monitoring. These patients have bronchoconstriction and significant airway inflammation, often have mucus hypersecretion and can rapidly develop respiratory failure. Most treatments initiated in the ED are continued during hospitalisation. Patients with impending respiratory failure should be transferred to the ICU.

Respiratory failure

Definition and presentation

The majority of patients hospitalised for asthma respond to medical therapy within the first few hours. In a minority, fatigue and unrelieved airway obstruction lead to respiratory failure.

On examination, patients may have difficulty speaking and, in the early stages before complete exhaustion, may demonstrate use of accessory muscles of respiration. Fatigue and airflow obstruction commonly present with decreased air movement, and wheezing may be difficult to auscultate. Exhaustion and gas exchange abnormalities may lead to altered consciousness, which should prompt the measurement of arterial blood gases. When respiratory effort is preserved, pulsus paradoxus may be evident. Tachycardia is common in the setting of respiratory distress and β-agonist treatment.

Hypoxaemia is uncommon and responds to minimal supplemental oxygen. Estimates of hypercarbia vary widely in the literature from 10% to 63%, and its presence signifies a significant obstructive ventilatory defect [63]. While hypercarbia is one manifestation of fatigue, it is not an absolute indication for mechanical ventilation [64].

Lactic acidosis in acute asthma is common and appears to reflect a direct effect of β-agonists on cellular metabolism rather than tissue hypoxia; its incidence and magnitude are correlated with serum albuterol levels [65]. The presence of lactic acidosis is not associated with worse

outcomes, but the acidaemia itself may contribute to dyspnoea, even when airway obstruction has improved. Arterial blood gas analysis along with serial lung function testing (bedside PEF or FEV_1) or measurement of airway resistance on a ventilator can help the clinician decide whether the ratio of acidaemia to obstruction warrants a reduction in β-agonist dose. β-agonist treatment may also lead to hypokalaemia, which should be monitored to prevent arrhythmias.

Mechanisms of respiratory failure

In the majority of fatal asthma cases, extensive mucus plugs fully occlude the airways [66]. These plugs increase airway resistance, thereby increasing the work of breathing and interfering with effective ventilation and gas exchange. Bronchoconstriction and airway oedema, along with changes in the airway walls from long-standing asthma, also contribute to airflow limitation. Together, these processes can result in an inability to fully empty the lungs during exhalation. This air trapping progressively increases functional residual capacity (hyperinflation), increases the work of breathing by placing tidal breaths into a low compliance region of the total lung capacity, and eventually decreases ventilation further. The increased intrathoracic pressure with hyperinflation can contribute to cardiovascular collapse and death. The proportion of cases of asthma with respiratory failure that have extensive mucus plugging or hyperinflation is unknown.

Management of respiratory failure

Patients who fail to improve after a few hours of medical therapy need close monitoring to detect worsening of respiratory, cardiac or neurological status, and require the availability of nurses, respiratory therapists and physicians to make rapid changes in therapy. This is best accomplished in the ICU, where there is also expertise with advanced interventions including noninvasive positive-pressure ventilation (NPPV) and invasive mechanical ventilation.

Role of NPPV

The availability and use of NPPV has increased dramatically over the past 15 years. NPPV is used to avoid intubation and to accelerate the response to medical therapy. Beyond these short-term responses, the goal is to reduce ICU or hospital length of stay and to increase survival. The most compelling data that NPPV can achieve these goals come from studies of COPD exacerbations with hypercapnic acidosis, which have consistently shown a significant reduction in the rate of intubation and in mortality, with purported mechanisms including offloading of respiratory muscles and prevention of dynamic airway collapse through PEEP [67].

A number of RCTs have examined whether NPPV can improve outcomes, including intubation rate and mortality, in severe acute asthma [68, 69]. Although none has definitively answered these questions due to low-power, supoptimal medical therapy and the use of rescue NPPV in the control group, studies have shown significantly greater and faster improvements in PEF and FEV_1 [68, 69], and one study demonstrated shorter ICU and hospital stays and smaller total doses of bronchodilator [70]. Bronchodilators can be delivered by placing the nebuliser between the leak port and the patient in order to maximise the delivered dose effectively [71, 72]. Bronchodilators can also be delivered during short breaks in NPPV [73].

In a retrospective analysis of 13 930 patients treated for acute asthma exacerbation across 97 hospitals, 9% of patients required some form of mechanical ventilation, 40% of whom received NPPV [74]. Older patients and those with a lower severe acute physiology score were more likely to receive NPPV than endotracheal intubation. The low rate of NPPV failure (4.7%) suggested that it was used primarily in a nonsevere population who would have improved regardless of this therapy. Although NPPV was associated with a lower risk of death in this propensity-matched analysis, the increased risk of death in the setting of NPPV failure underscores the need for careful monitoring.

The possibility of shorter hospital stays and reduced doses of bronchodilator may be desirable to payers and patients, but there are a number of issues to consider in the application of NPPV. Some patients with severe acute asthma, respiratory distress and the associated anxiety are intolerant of a tight-fitting mask, and patients whose exacerbations are characterised by sputum production may have difficultly clearing secretions while wearing a mask delivering positive pressure. Further studies are needed to address optimal inspiratory and expiratory pressures and how early in the course of an exacerbation NPPV should be applied. An important variable in deciding when to apply NPPV is the increased nursing and respiratory therapist time involved in set-up, adjustment and monitoring; this lost time can be an opportunity cost in other aspects of patient care if NPPV is applied too early or for inappropriately mild exacerbations. While it may seem that early NPPV use, even in mild cases, may at best lead to no harm, there is reason to be concerned about such an approach. Positive pressure may accelerate hyperinflation and contribute to large tidal volumes, which may increase the risk of developing lung injury. Finally, the usual contraindications to positive-pressure mask therapy apply in the setting of asthma as well: these are difficulty in managing secretions, nausea and vomiting, altered consciousness and cardiovascular instability.

In summary, without evidence from trials for a benefit in patient outcomes, NPPV can be given to patients with an inadequate response to early medical therapy, who can cooperate with positive pressure through a mask and who do not have contraindications including a need for immediate endotracheal intubation. In the absence of further data, the settings used in one RCT provide a reasonable place to start (table 3) [73]. There is a theoretical concern for worsened hyperinflation with the resistance to emptying from positive airway pressure and, although none of the trials to date has reported this as a complication, it is reasonable to be cautious of high expiratory pressures. NPPV should be used only in an environment with experienced nurses and respiratory therapists, and where patients are constantly monitored and can be intubated immediately if required.

Endotracheal intubation and invasive mechanical ventilation

Rates of intubation for severe acute asthma vary widely, probably reflecting variations in the populations studied (*e.g.* in pre-hospitalisation care and social/genetic determinants of disease) and the variable thresholds of individual centers and practitioners as well as their resources to intubate. In a recent study of ~750 000 admissions across the USA, 7.4% required intubation, and rates were higher during the autumn and winter months [75]. Two prior analyses of US databases of 30 000 and 65 000 admissions for asthma exacerbations reported lower rates of intubation of 2.1% and 4.2%, respectively [76, 77].

The decision to intubate is made by the same criteria used in other cases of respiratory failure: exhaustion, significantly abnormal gas exchange including progressive hypercapnia

Table 3. Summary and recommendations for noninvasive positive-pressure ventilation (NPPV)

Evidence-based benefits of NPPV
Faster improvement in PEF and FEV_1; decreased dose of bronchodilators and reduced hospital stay in one study only [70]
Recommended settings [73]
Start with IPAP 8 cmH_2O, EPAP 3 cmH_2O
Small increases (2 cmH_2O IPAP, 1 cmH_2O EPAP) every 15 min targeting a reduction in respiratory rate and improvement in gas exchange
Limit EPAP to 5 cmH_2O, given a theoretical concern for worsening hyperinflation
Contraindications
Difficulty managing secretions, nausea and vomiting, altered consciousness and cardiovascular instability

PEF: peak expiratory flow; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure.

despite current therapy, cardiovascular instability and airway protection for depressed consciousness. An addition to this list specific to asthma is the presence of a silent chest, which is a consequence of severe airway obstruction, hyperinflation and exhaustion. Importantly, while a progressively increasing $PaCO_2$ with mental status changes is an indication for intubation, hypercarbia by itself does not mandate intubation [64].

Recommendations for the intubation procedure

We recommend following the widely accepted core principles of safe intubation. Adequate pre-oxygenation, laryngoscopy equipment familiar to the proceduralist and backup plans for an unanticipated difficult airway are essential. Consensus opinion favours the induction of general anaesthesia and paralysis with rapid-sequence intubation [78]. This opinion stems in part from the wide familiarity with this approach, the high rates of success in emergency situations and the minimisation of aspiration risk. Although awake fibreoptic intubation is attractive, given the preservation of ventilation and lack of paralysis, it can be difficult in the setting of respiratory distress due to patient discomfort and inadequate topical anaesthesia, and should be performed only by those highly experienced in this technique. Oral intubation is preferred over the nasopharyngeal route given the coexistence of rhinosinusitis and nasal polyps with asthma and the desire to use the largest tube possible to facilitate removal of airway secretions.

Given that increased intrathoracic pressure due to hyperinflation may be present, the sympatholytic, vasodilatory and myocardial suppressant effects of induction agents warrant anticipation of and readiness to address hypotension. Prior to induction, dehydration should be corrected with judicious use of intravenous fluids, and a vasopressor such as norepinephrine or phenylephrine should be ready to administer.

There are many valid choices for drugs to induce anaesthesia at the time of intubation. Ketamine has a theoretical advantage of promoting bronchodilation by releasing catecholamines and directly relaxing airway smooth muscle; it is also not expected to cause hypotension. It is unclear whether the potential risks of hypersecretion necessitate pre-treatment with an anti-sialogogue. The use of ketamine is relatively contraindicated in the setting of significant hypertension and ischaemic heart disease, and controversy

remains regarding its contribution to increased intracranial pressure in the setting of brain injury. Propofol has the advantage of very fast on and off kinetics, along with a few reports of bronchodilatory effects [78]; however, hypotension may limit the dose. Etomidate has the fewest haemodynamic effects and is an acceptable alternative in the setting of hypotension; despite its association with adrenal suppression, a single dose does not appear to cause harm [79]. While benzodiazepines are also successful in achieving rapid induction of anaesthesia, the high doses required are frequently associated with hypotension. Opiates, especially morphine, are generally avoided during induction, due to concern over histamine release and the associated increase in bronchoconstriction, although they may be warranted in cases of advanced myocardial dysfunction or elevated intracranial pressure where sympathetic responses from pain during intubation need to be blunted.

Neuromuscular paralysis simultaneous with the induction of anaesthesia is a key feature of rapid-sequence intubation, and improves the ability to visualise and intubate the glottis. Succinylcholine has the advantages of a rapid onset and short duration of paralysis, but concerns about its ability to raise potassium levels, which contribute to arrhythmias, and to release histamine, which worsens bronchospasm, have led to greater use of nondepolarising agents. The nondepolarising agents (*e.g.* vecuronium and rocuronium) are longer acting and therefore substantially increase the risk of hypoxia if there is difficulty intubating. Regardless of the agent chosen, the risks associated with paralysis warrant an assessment of the ability to intubate and ventilate before the procedure begins.

Ventilator settings

Two major concepts in ventilator management guide the choice of settings in an asthma exacerbation. The first is that expiratory times too short to allow for complete exhalation lead to progressive hyperinflation (figure 3a). Short expiratory times occur when the ventilator is set to have high minute ventilation through an increased respiratory rate or tidal volume, or both. Seminal studies in the 1980s raised awareness of the increased risk of hypotension, barotrauma (*e.g.* pneumothorax) and death from dynamic hyperinflation when the ventilator was adjusted in this way to normalise arterial carbon dioxide [81, 82]. It was found that correcting hypoxaemia with supplemental oxygen without attempting to normalise alveolar ventilation led to decreased hyperinflation and an improvement in all of these outcomes. Hypercarbia is usually tolerated and, except in cases with elevated intracranial pressure or myocardial dysfunction, ventilator settings should aim to reduce hyperinflation rather than correct arterial carbon dioxide. As airflow obstruction improves, hypercarbia will naturally improve. Volume-targeted modes are preferred in asthma exacerbations due to the variable tidal volumes delivered in pressure-targeted modes as the degree of airflow obstruction changes. A constant inspiratory flow (rather than decelerating ramp) is recommended in order to decrease inspiratory time, leaving more time for exhalation.

Hyperinflation is recognised through inspection of flow and pressure waveforms, which may show an inhalation that starts before expiratory flow returns to zero, elevated plateau pressure (P_{plat}, measured during an inspiratory pause) or high auto-PEEP (measured during an expiratory pause) (figure 3b and c). If hyperinflation is present, the ventilator should be adjusted to prolong the expiratory time by decreasing the respiratory rate or lowering the inspiratory time; in volume-targeted modes, a lower inspiratory time is achieved by increasing the inspiratory flow rate and decreasing the tidal volume. Targeting a respiratory rate of 10–14 breaths·min^{-1} with minute ventilation of <10 L·min^{-1} reduces

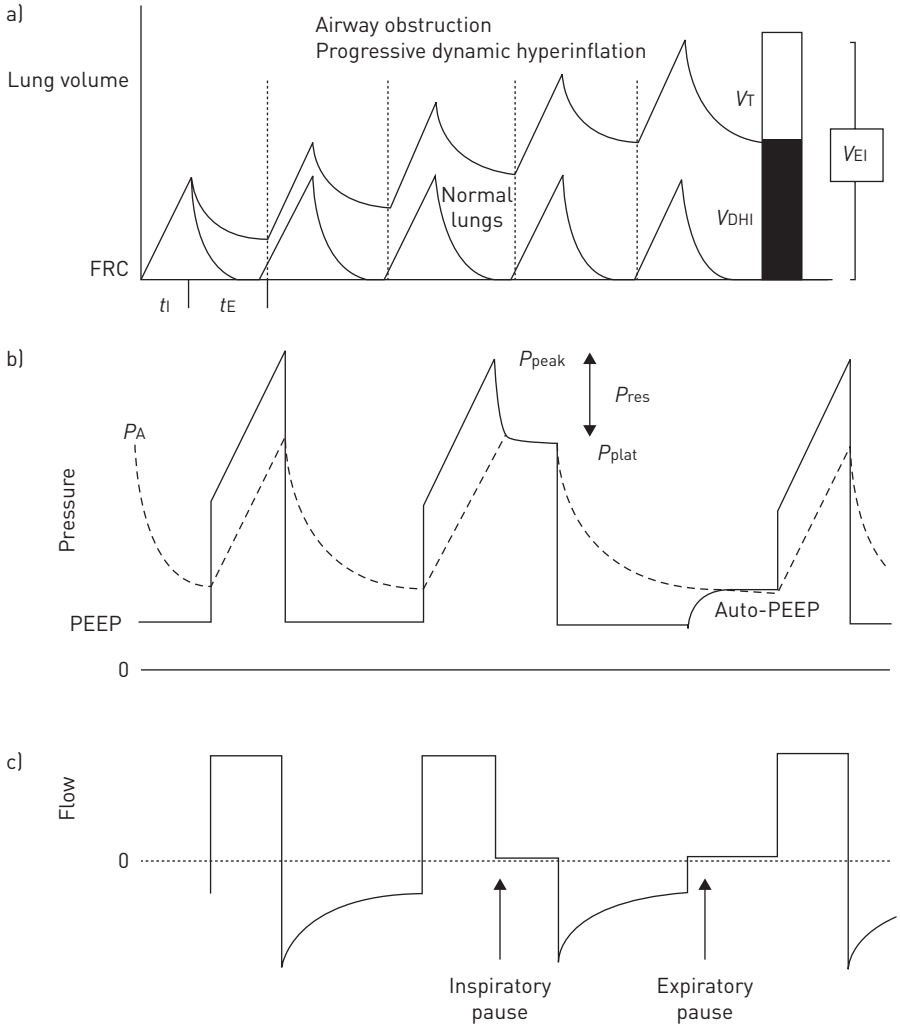

Figure 3. a) Graphical representation of the development of dynamic hyperinflation, indicated by a rise in end-expiratory lung volume above functional residual capacity (FRC) due to inadequate time for complete exhalation of tidal volume (V_T). b and c) Schematic representation of b) airway pressure and c) flow during controlled mechanical ventilation. Note that flow persists at end-expiration, indicating that end-expiratory alveolar pressure (P_A) exceeds circuit pressure (*i.e.* auto-PEEP is present). The dashed line represents P_A. t_I: inspiratory time; t_E: expiratory time; V_{DHI}: volume (above FRC) caused by dynamic hyperinflation; V_{EI}: volume (above FRC) at end inspiration; P_{peak}: peak airway pressure; P_{res}: inspiratory flow-resistive pressure; P_{plat}: plateau airway pressure. Reproduced from [80] with permission.

the risk of hypotension and barotrauma [82]. There are few data to dictate threshold pressures below which the risk of negative outcomes is minimised. In line with recommendations from the field of ventilator-induced lung injury, there is a low incidence of hypotension and barotrauma when P_{plat} is <30 cmH_2O [78]. Interpretation of P_{plat} should take into account factors such as reduced chest wall compliance (*e.g.* in obesity), which will lead to overestimation of transpulmonary pressure through P_{plat}, and heterogeneity in lung compliance, which will lead to some areas experiencing much higher stress than indicated by P_{plat}. A goal of keeping auto-PEEP at <10 cmH_2O is reasonable, with the recognition that forced exhalation can cause overestimation of auto-PEEP and airway closure can cause underestimation. There are no data available to suggest that

increasing the set PEEP offers benefits in terms of reduced work to trigger the ventilator or to keep airways open, as it might in COPD; in the absence of significant hypoxaemia, set PEEP should be $\leqslant$5 cmH_2O to minimise resistance to exhalation.

The second, evidence-based principle to follow is avoidance of large tidal volumes to reduce the risk of ventilator-induced lung injury. Numerous studies have demonstrated a reduction in lung injury and mortality when low tidal volumes ($\leqslant$6 $mL{\cdot}kg^{-1}$ of predicted body weight) are used in ARDS [83]. In asthma and other obstructive diseases, the goal to reduce tidal volume to prevent lung injury, which sometimes necessitates higher respiratory rates to ensure adequate minute ventilation, needs to be balanced by the need to allow adequate time for exhalation to prevent air trapping. On balance, it is reasonable to target a tidal volume of $\leqslant$8 $mL{\cdot}kg^{-1}$ of predicted body weight in the setting of an asthma exacerbation. Table 4 provides recommended ventilator settings.

Pharmacological treatment during mechanical ventilation

Discomfort from the endotracheal tube or dyssynchrony between patient and the ventilator requires sedation. Ventilator dyssynchrony contributes to breath stacking and hyperinflation if there is inadequate time for exhalation, and must be addressed to prevent barotrauma and hypotension. If sedation is required once pain is adequately treated, we recommend a continuous infusion of propofol, given its short duration of action and associated decreased risk of delirium and prolonged intubation compared with benzodiazepines [84]. Boluses or an infusion of benzodiazepines may be required when propofol is not tolerated due to hypotension, hypertriglyceridaemia or concern about propofol infusion syndrome. In cases where agitation or anxiety is driving a mild degree of dyssynchrony, a dexmedetomidine infusion may be all that is needed; similar to propofol, dexmedetomidine has a short duration of action and also induces hypotension (but, unlike propofol, induces bradycardia as well). Regardless of the sedation agent chosen, opiates are useful adjuncts to suppress respiratory effort. Fentanyl is preferred over morphine, which has the potential for histamine release. Sedation with ketamine is appealing, given the potential for additional bronchodilation and lack of associated hypotension. However, there is a substantial risk of dysphoric reactions with ketamine when it is used at sedating doses. Furthermore, at subdissociative continuous infusion doses, one RCT showed no benefit in symptoms, lung function, respiratory rate or the rate of hospital admission when ketamine was given in the ED to spontaneously breathing patients [85], and only case reports suggest a benefit in the setting of mechanical ventilation [86, 87]. Finally, one must consider

Table 4. Recommendations to prevent hyperinflation on mechanical ventilation

Ventilator settings	
	Respiratory rate 10–14 $breaths{\cdot}min^{-1}$, V_T 8 $mL{\cdot}kg^{-1}$ of PBW, adequate time to exhale, PEEP $\leqslant$5 cmH_2O
Sedation	
	Deep sedation may be required in some cases to prevent dyssynchrony and hyperinflation
Paralysis	
	Use only if hyperinflation cannot be managed with the above, given the risk of myopathy and neuromuscular weakness

V_T: tidal volume; PBW: predicted body weight.

whether the patient's obstruction has improved enough such that, rather than increased sedation, the best change to counter dyssynchrony is to convert to a spontaneous mode of breathing (see section on Liberation from mechanical ventilation).

Ongoing neuromuscular paralysis should only be used if there is difficulty in achieving stability with adjustment of the ventilator and increases in sedation. Based on retrospective data, concern remains about an increased risk of myopathy with the addition of neuromuscular blockade to corticosteroid therapy. In one study, with each additional day of muscle relaxation, there was an OR of 2.1 (95% CI 1.4–3.2) for the development of myopathy [88]. We recommend limiting the duration of paralysis by weaning from it early and continuing deep sedation if needed.

Bronchodilators are effective in mechanically ventilated patients. Although the tubing and humidification in the ventilator circuit contribute to loss of drug, the few data available have found that, as long as the dose is adjusted accordingly, MDIs and nebulisers are effective and equivalent. Guidelines for optimising bronchodilator delivery in mechanically ventilated patients are available [78].

Nonstandard therapies

Some nonstandard therapies are given in table 2. The pathology of fatal asthma suggests that efforts to mechanically and pharmacologically remove and break down mucus can improve outcomes, at least if the mucus is proximal enough to be affected. Bronchoscopy with or without simultaneous instillation of a mucolytic such as *N*-acetylcysteine or recombinant human DNase has been reported anecdotally to improve obstruction [80]. However, no RCTs exist to evaluate the benefits of these interventions and, given the possibility of airway irritation with these procedures, we recommend against routine use. They can be considered in the setting of refractory respiratory failure or if there is concern for an airway lesion, such as when focal wheezing or lobar collapse is present. Similarly, there are no data to suggest a benefit from heliox during mechanical ventilation. Case reports suggest that ECMO, and the less invasive modality of extracorporeal carbon dioxide removal, can be considered in severe hypoxaemia or hypercarbia refractory to standard management, especially if barotrauma is already present. Rarely, volatile anaesthetics with bronchodilatory properties are used for cases of refractory bronchoconstriction if trained personnel and specialised gas-conserving systems are available in the ICU. Case reports and small, uncontrolled studies suggest a benefit to using inhaled anaesthetics, but the treatment remains experimental [78, 80].

Outcomes of mechanical ventilation

Patients requiring endotracheal intubation and mechanical ventilation have a higher mortality rate (5–20%) compared with non-intubated cases (<1%) of inpatient asthma exacerbations [75–78]. It is unknown how much of this is due to increased severity of the disease and associated consequences (*e.g.* pre-hospital cardiac arrest and cerebral anoxia) *versus* the adverse effects of critical care (*e.g.* barotrauma, hypotension, nosocomial pneumonia, sepsis, gastrointestinal bleeding, deep venous thrombosis and neuromuscular weakness) mediated by mechanical ventilation, sedation, immobility and indwelling catheters. Preventative measures such as ventilator bundles, minimisation of sedation, early mobilisation, and attention to catheter care and removal may reduce the harm associated with mechanical ventilation. Fortunately, the data suggest that a ventilator strategy that

minimises hyperinflation and lung injury reduces the complications and mortality associated with mechanical ventilation [89].

Liberation from mechanical ventilation

The duration of mechanical ventilation and determinants thereof are understudied. In one report, patients were intubated for 3.4±3.8 days on average [89]. Many patients require ⩽48 h of mechanical ventilation, consistent with the reversible nature of airway obstruction and the responsiveness to medications in asthma. The aetiology of asthma exacerbation and the pre-hospital course have an impact on the duration to improvement once intubated. In cases where the duration of symptoms preceding hospital admission is short, such as with inhalation of irritants, including cocaine, the duration of intubation is significantly shorter than in patients with other aetiologies of exacerbation [89]. Patients with more significant mucus impaction, as might be expected to occur with infection or high levels of allergic, type-2 inflammation, may have both a longer prodrome and a longer duration of intubation. A spontaneous breathing trial should be done in awake patients and extubation considered when there is no evidence of hyperinflation, airway resistance has improved (<20 $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$), P_{aCO_2} has normalised and patients can handle secretions with an effective cough. Difficulty weaning or post-extubation failure should lead to expansion of the differential diagnosis to include neuromuscular weakness (from corticosteroids, neuromuscular blockade, critical illness or hypophosphataemia), vocal cord dysfunction, laryngospasm, tracheobronchomalacia, airway lesions, and parenchymal, vascular or pleural lung disease.

Discharge from the hospital

Careful discharge planning has the potential to reduce the high risk of relapse after an exacerbation. Patients should use SABAs as needed and continue oral corticosteroids for 5–7 days [14, 15, 43, 44]. The risk of relapse is reduced when patients are discharged with ICSs [90, 91]. Although the data do not provide guidance on whether there is any benefit to adding ICSs during the hospital stay, earlier initiation does give patients time to practise administration. Exacerbations of asthma often indicate inadequate therapy, improper use of medications, poor adherence or lack of an action plan to respond to early changes in asthma control. Therefore, during hospitalisation and discharge, providers and patients should review inhaler technique, and develop plans to minimise exposure to environmental triggers and to self-adjust medications in response to changes in symptoms or PEF. Samples of action plans and other educational materials are available in expert guidelines [14]. In addition to an action plan, expert guidelines also recommend that patients follow up with their primary care provider or an asthma specialist within 1–4 weeks of discharge from the ED or hospital, and they are encouraged to call a provider if there are problems with asthma control in the first 3–5 days after discharge.

Future directions

Phenotypes of asthma delineated by dysregulation in immune responses and molecular pathways in lung-resident cells have refined the care of asthma in the outpatient setting. Recognition of the variable presence of type-2 airway inflammation has led to targeted therapies that reduce the number of exacerbations and improve lung function [92]. Studies on how these molecular phenotypes and associated biomarkers can inform the

management of asthma exacerbations in the hospital are lacking. The growing recognition of an overlap in features of asthma and COPD, the unique characteristics of asthma in the setting of obesity, and the presence of severe, fixed airflow obstruction are additional phenotypes that warrant study of their impact on care of the hospitalised patient. The observation of marked mucus impaction in fatal asthma suggests a potential for high impact from the development of more effective mucolytic strategies.

Conclusion

Worldwide, acute asthma exacerbations account for a high proportion of urgent healthcare visits. Although self-management at home may avert some of these visits, patients who present for evaluation require immediate attention. Medical treatment is directed towards rapid reversal of airflow obstruction with β_2-agonists to relax airway smooth muscle, corticosteroids to decrease inflammation and supplemental oxygen to correct hypoxaemia. Beyond these medications, muscarinic antagonists may provide some benefit prior to hospital admission, but other therapies, including magnesium, leukotriene modifiers, methylxanthines, heliox and antibiotics, are not supported by published evidence. Lack of significant early improvement should prompt hospital admission. It is important to recognise impending respiratory failure and admit these patients to the ICU, where mechanical assistance with ventilation can be provided. NPPV may accelerate recovery in some patients but does not appear to prevent intubation; the ideal candidate for NPPV and the best timing need to be better defined. With the use of modern strategies to intubate and mechanically ventilate the asthmatic patient, and the increased attention to minimising nosocomial harm, hospital morbidity and mortality are low. Nonetheless, exacerbations often signal the need for more intensive disease management in the outpatient setting. In order to prevent relapse, every attempt should be made to provide education and optimise access to medications and providers prior to discharge.

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Chapter 6

Hypercapnic respiratory failure in non-COPD

Neeraj M. Shah[1,2] and Patrick B. Murphy[1,2]

This chapter discusses the pathophysiology of hypercapnic respiratory failure in conditions other than COPD. First, the development of alveolar hypoventilation is explained, and the load–capacity–drive model of hypercapnic respiratory failure is described. An increase in respiratory load or a decrease in respiratory muscle capacity or neural drive will lead to alveolar hypoventilation. This model is used to explain the pathophysiology of hypercapnic failure in acute and chronic neuromuscular diseases and obesity hypoventilation syndrome. It is outside the scope of this chapter to comprehensively discuss the management of these conditions; however, key concepts related to the management of acute deteriorations and hypoventilation are outlined. Other causes of alveolar hypoventilation, such as cystic fibrosis and chest wall disorders, are discussed briefly.

Respiratory failure occurs when there is inadequate exchange of oxygen and carbon dioxide to meet the requirements of metabolism. Hypoxaemic (type I) respiratory failure occurs when disease processes impair oxygen transfer, leading to insufficient oxygen levels in the blood. Hypercapnic (type II) respiratory failure occurs when inadequate alveolar ventilation (V'_A) leads to the failure to clear carbon dioxide.

The most common cause of hypercapnic respiratory failure is COPD, which is discussed in another chapter in this *Monograph* [1]. This chapter will focus on the pathophysiology of hypercapnic failure in other important conditions leading to respiratory morbidity, including neuromuscular disorders (NMDs) and obesity hypoventilation syndrome (OHS). First, it is important to understand the fundamental pathophysiology of hypercapnic respiratory failure, before applying these fundamentals to each condition.

Pathophysiology of hypercapnic failure

As already mentioned, V'_A is crucial for the removal of carbon dioxide from the blood. V'_A, carbon dioxide production (V'_{CO_2}) and P_{aCO_2} are linked *via* the following equation:

$$V'_A = V'_{CO_2} / P_{aCO_2} \times K$$

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where K is a constant that takes into account the different units of V'_A, V'_{CO_2} and P_{aCO_2}.

This can be rearranged as:

$$P_{aCO_2} = V'_{CO_2}/V'_A \times K$$

In other words, as V'_A decreases, P_{aCO_2} will increase, *i.e.* P_{aCO_2} is inversely proportional to V'_A. Factors that contribute to inadequate V'_A are reduced minute ventilation (V'_E) and increased dead space. V'_E is the sum of dead space ventilation (V'_D) and V'_A:

$$V'_E = V'_D + V'_A$$

Alternatively:

$$V'_A = V'_E - V'_D$$

Under normal conditions, V'_E is controlled by ventilatory drive, which adjusts respiratory muscle pump function to match metabolic activity, to maintain adequate carbon dioxide clearance. Thus, adequate V'_E requires integrity of the neural pathway from the central respiratory centre to the respiratory musculature, and satisfactory force generation, as well as coordination of the respiratory muscles. The numerous causes of alveolar hypoventilation can be considered according to this anatomical framework.

Central respiratory depression is caused by any higher-level lesion such as stroke, a space-occupying mass or haemorrhage, as well as drugs (*e.g.* anaesthetics, benzodiazepines, opiates) and spinal cord lesions.

Many conditions can interrupt the pathway from the central drive in the medulla to the respiratory musculature. Upper motor neurons can be affected by a cervical cord lesion (*e.g.* trauma, tumour, demyelination or syringomyelia). Complete spinal cord lesions above C4 produce phrenic nerve dysfunction whereas a fracture-dislocation of the lower cervical spine will lead to interrupted function of the intercostal and expiratory muscles (but will spare the diaphragm). Conditions affecting the anterior horn cell (*e.g.* poliomyelitis, amyotrophic lateral sclerosis, spinal muscular atrophies), lower motor neuron (*e.g.* trauma, motor neuron disease, Guillain–Barré syndrome) and the neuromuscular junction (*e.g.* myasthenia gravis, botulism toxin, drugs such as anaesthetics or organophosphates) can all lead to impaired ventilation and hypercapnia. Figure 1 displays this anatomical pathway.

Conditions directly affecting the respiratory musculature will result in unsatisfactory force generation. These include muscular dystrophies, critical care myopathy and the hyperinflation of COPD, which results in poor contractility due to a mechanically disadvantaged diaphragm. Finally, conditions that result in reduced compliance of the chest wall (*e.g.* kyphosis, scoliosis, obesity, contracted burn scars) or the lungs (*e.g.* fibrosis, acute lung injury, empyema) can also result in impaired ventilation.

A useful framework to use when considering the contribution of disease processes to hypercapnic respiratory failure is the load–capacity–drive model (figure 2) [2]. Respiratory

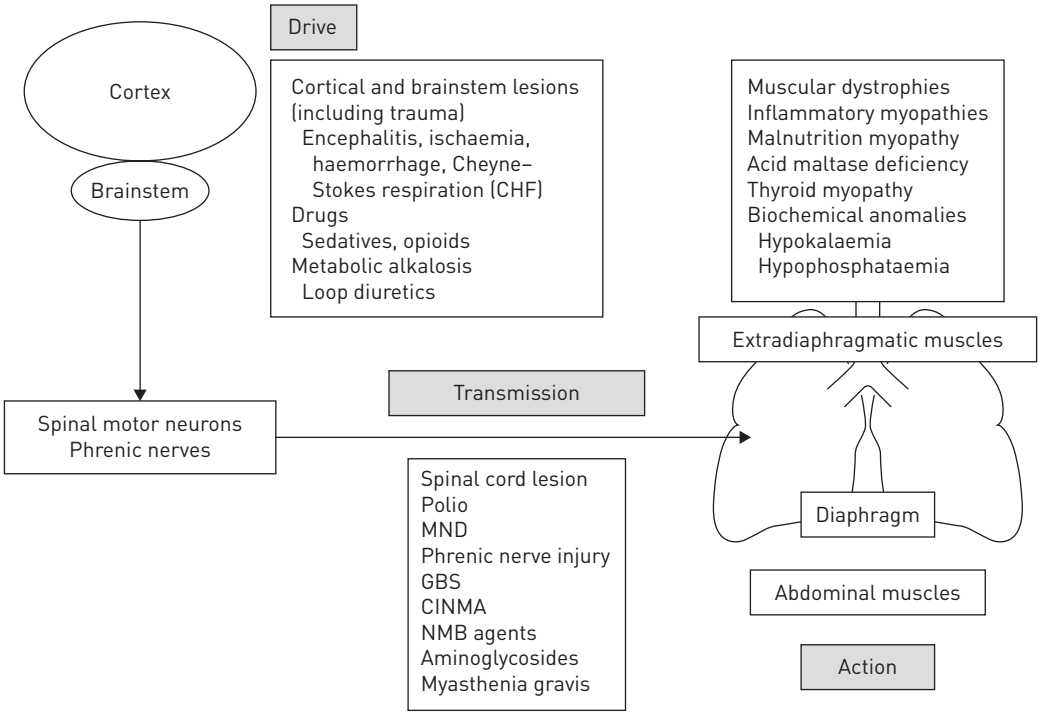

Figure 1. Schematic diagram representing the anatomical distribution of possible pathological lesions disrupting the respiratory muscle load–capacity–drive system. CHF: congestive heart failure; MND: motor neuron disease; GBS: Guillain–Barré syndrome; CINMA: critical illness neuromuscular abnormality; NMB: neuromuscular blocking.

load refers to the combination of resistive load (airways resistance to airflow), elastic load (inversely proportional to compliance) and threshold load (intrinsic PEEP). Load can be quantified using invasive pulmonary mechanics to measure oesophageal pressure, as a surrogate for pleural pressure, and air flow during the respiratory cycle. Load is increased in airway obstruction and hyperinflation (*e.g.* COPD, asthma, cystic fibrosis), stiff lungs (*e.g.*

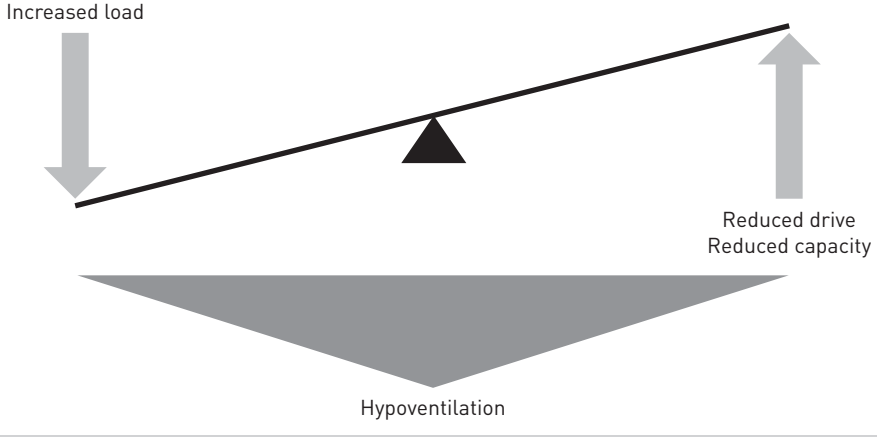

Figure 2. The respiratory muscle load–capacity–drive model. Alveolar ventilation is determined by the balance between respiratory load, muscle capacity and neural drive. An increase in load, or a decrease in muscle capacity or neural drive, will result in hypoventilation and respiratory failure.

fibrosis, pulmonary oedema) and chest wall disease (*e.g.* obesity, kyphoscoliosis, pleural disease). Excessive respiratory load can be overcome by driving the respiratory muscle pump harder; however, at sufficient loads the system moves to prevent fatigue by reducing tidal volume, with the subsequent development of hypoventilation and hypercapnia. Respiratory muscle capacity is a measure of inspiratory respiratory muscle strength and endurance. Global respiratory muscle strength can be assessed by measuring the maximum inspiratory mouth pressure or the sniff nasal inspiratory pressure. Diaphragm-specific function can be assessed using the transdiaphragmatic pressure (Pdi) produced during these manoeuvres (figure 3). Capacity is reduced by direct respiratory muscle weakness or indirectly by adverse pulmonary mechanics, such as hyperinflation in COPD. If there is insufficient respiratory muscle capacity, V'A decreases and hypercapnic failure will ensue. Finally, respiratory drive is the process by which the respiratory centre in the medulla controls the rate and work of breathing in response to pH and PaCO_2. The spinal cord is the conduit of this response to the muscles of respiration. Without adequate respiratory drive and passage of neural information to the muscles of respiration, there will be no stimulus to respond to increased PaCO_2, resulting in hypercapnic failure. Acute acidosis has been demonstrated to be deleterious to pulmonary function, leading to diminished diaphragm contractility [3–5], reducing respiratory muscle capacity and thereby further exacerbating ventilatory failure. Table 1 displays conditions causing hypercapnic respiratory failure with the anatomical source of failure and their impact on the load–capacity–drive model.

When discussing NMDs and OHS, this framework will be used to demonstrate how they each lead to hypercapnic failure in both the chronic and acute settings.

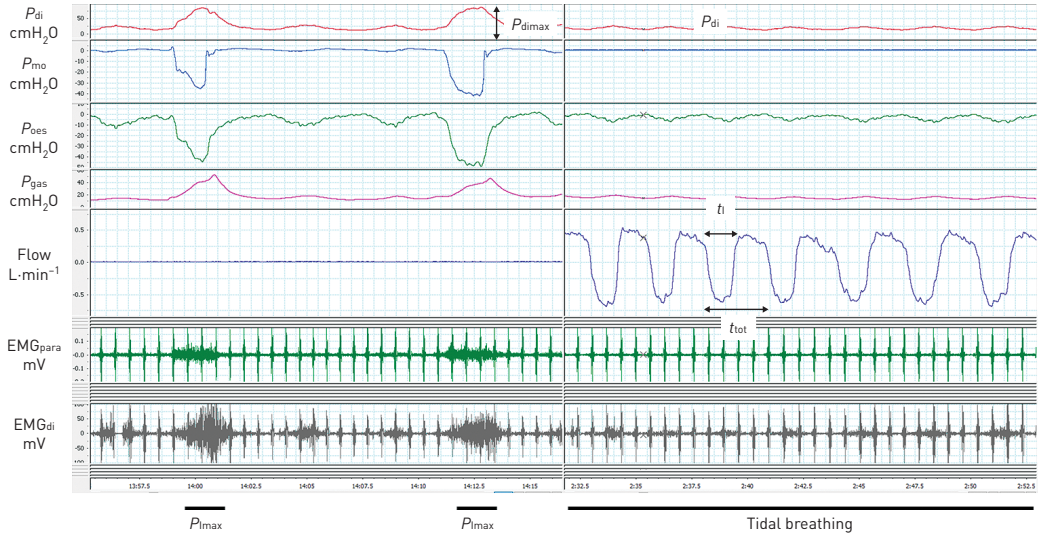

Figure 3. Invasive pulmonary mechanics. This figure is an example of invasive pulmonary mechanics recorded in a healthy individual. Pressure recordings, followed by flow measurement and finally electromyogram traces are displayed, initially during a maximal inspiratory pressure (PImax) manoeuvre, and then during tidal breathing. Pdi: transdiaphragmatic pressure (the pressure the diaphragm produces during tidal breathing); Pdimax: maximal pressure the diaphragm can generate, displayed here during a PImax manoeuvre; Pmo: mouth pressure; Poes: oesophageal pressure; Pgas: gastric pressure; tI: inspiratory time (the time the diaphragm is contracted); $t$tot: length of the total respiratory cycle; EMGpara: parasternal electromyogram; EMGdi: diaphragmatic electromyogram.

Table 1. Conditions causing hypercapnic respiratory failure

Anatomical region affected	Condition	Effect on load–capacity–drive
Central nervous system	Brainstem lesion	Reduced drive
	Opiates/benzodiazepines	Reduced drive
	Cervical cord lesion	Reduced drive
Peripheral nervous system	Poliomyelitis	Reduced capacity
	Motor neuron disease	Reduced capacity
	Guillain–Barré syndrome	Reduced capacity
Neuromuscular junction	Myasthenia gravis	Reduced capacity
	Botulism	Reduced capacity
	Organophosphates	Reduced capacity
Muscle	Muscular dystrophies	Reduced capacity
Chest wall	Obesity hypoventilation syndrome	Increased load
	Kyphoscoliosis	Increased load
	Pulmonary fibrosis	Increased load
Airway	Cystic fibrosis	Increased load

Conditions are categorised according to the anatomical region they affect, and the load–capacity–drive model is used to illustrate how each condition leads to hypercapnic failure.

Neuromuscular disorders

Chronic NMDs

The term "neuromuscular disorder" encompasses a wide range of progressive neurological diseases that can affect the respiratory system. While these conditions are rare, with a prevalence of one to 10 per 100 000 population [6], they can develop significant respiratory morbidity, which is often the cause of death [7, 8]. The likelihood of respiratory failure in NMDs is dependent on the pattern of muscle involvement; conditions most commonly associated with respiratory failure include motor neuron disease, spinal muscular atrophy, myasthenia gravis and the muscular dystrophies. These disorders cause respiratory dysfunction *via* respiratory pump failure, impaired cough function by affecting the inspiratory, expiratory and glottic muscles, and upper-airway dysfunction by affecting glottic muscles. This chapter focuses on their effect on ventilatory function; however, it is important to have an appreciation of their effect on cough and upper-airway function to understand the cause of acute deterioration.

NMDs cause hypercapnic respiratory failure by four routes: 1) respiratory muscle weakness; 2) altered respiratory mechanics; 3) abnormal central control of breathing; and 4) non-respiratory means [9]. Respiratory muscle weakness in NMDs is associated with increased susceptibility to muscle fatigue. In order to counter this risk, patients adopt a rapid, shallow breathing pattern, which reduces tidal volume by minimising inspiratory time (t_I) and P_{di}. While this will reduce the risk of muscle fatigue, it is at the expense of hypercapnia [10].

NMDs tend to result in increased elastic recoil and therefore reduced respiratory compliance. The rapid shallow breathing pattern adopted by patients with NMDs has been demonstrated to reduce chest wall compliance [11]. Fibrosis of the rib cage muscles in muscular dystrophies [12] will further reduce compliance and limit inspiratory capacity. Similarly, spinal deformities found in many NMDs will also reduce compliance [13]. Poor

pharyngeal dilator muscle function, seen in many NMDs, will result in reduced upper-airway calibre and so will increase upper-airway resistance in inspiration. This produces a higher load on the diaphragm in inspiration and so increases the work of breathing. Combined with the decreased upper-airway tone in sleep, this leads to the development of sleep-disordered hypoventilation [14–16].

Sleep-disordered breathing is prevalent in NMDs and has been reported as having an incidence of between 10.3% and 61.2%, depending on the definition [17]. Sleep-disordered breathing leads to impaired central respiratory drive in NMDs [18, 19], which may be caused by loss of sensitivity to P_{aCO_2} [7]. This reduced drive leads to a gradual build-up of carbon dioxide, resulting in hypercapnic respiratory failure. As many NMDs affect the central nervous system, they may have a direct effect on the central respiratory centre, independent of sleep-disordered breathing. It is difficult to elucidate this, as usual measures of central drive, such as airway occlusion pressure ($P_{0.1}$), are affected not only by central drive but also by respiratory muscle weakness and deranged respiratory mechanics, all of which are seen in NMDs [20].

Many NMDs are associated with cardiomyopathies [21], leading to left ventricular failure [22]. Resultant pulmonary venous congestion reduces pulmonary compliance and therefore increases the work of breathing. Recent evidence suggests that heart failure impairs pulmonary muscle blood flow [23], suggesting that pulmonary muscle blood flow will also be impaired in patients with neuromuscular cardiomyopathy, exacerbating respiratory muscle dysfunction. Some patients with NMDs are overweight due to poor dietary habits, sedentary status and steroid use [24]. Increased abdominal adiposity places a significantly increased load on the respiratory system, and favours the development of hypoventilation in sleep. The implications of obesity and hypoventilation on the respiratory system are discussed in more detail in a later section of this chapter. Patients with NMDs may also be poorly nourished due to disorders of the gastrointestinal tract and musculature [25]. Poor nutrition is associated with diaphragmatic atrophy [26], and this may independently contribute to poor respiratory pump function, with increased risk of adverse respiratory morbidity [27].

Patients with NMDs frequently present with acute respiratory deterioration. This is usually due to a combination of aspiration secondary to oropharyngeal muscle weakness, cough weakness causing impaired secretion clearance and respiratory muscle fatigue leading to hypoventilation. Oropharyngeal muscle weakness caused by the direct effect of the NMD on the musculature [28] weakens the ability to swallow and to protect the airway, increasing the risk of aspiration and recurrent infections.

Individuals need an effective cough to clear secretions. The production of an effective cough involves several respiratory muscles. Upon stimulation of the cough reflex, the diaphragm and external intercostal muscles contract to create a negative pressure around the lung. This allows air to enter the lungs to equalise the pressure, which stimulates closure of the glottis. The abdominal muscles then contract to accentuate the action of the relaxing diaphragm, while other expiratory muscles contract. This action combines to increase the pressure inside the lungs, which stimulates the glottis to relax, allowing air to be projected through the upper respiratory tract and expelled into the atmosphere. Therefore, patients with weakening of any of these muscles due to neuromuscular pathology will have reduced cough strength, causing difficulties with clearing respiratory secretions adequately. This impaired secretion clearance can lead to respiratory infections, and acutely can cause small-airway occlusion with subsequent ventilation–perfusion mismatch adversely affecting pulmonary mechanics. Worsening of the ventilation–perfusion mismatch will eventually lead to hypercapnic respiratory failure [29].

As well as presenting with infections, patients with NMDs can present acutely with hypercapnic failure. This is usually due to respiratory muscle fatigue. As the diaphragm performs the majority of inspiratory work at rest [30], diaphragmatic fatigue also has the most significant role in ventilatory failure in NMD patients. Diaphragmatic fatigue occurs within 60 min if: 1) the ratio of the time the diaphragm must contract (tI) to the total respiratory cycle ($t$tot) is 0.5, or 2) the pressure the diaphragm needs to produce for tidal breathing (Pdi) is >40% of the maximum pressure it can generate (Pdimax) [31]. Figure 3 shows a representation of invasive pulmonary mechanics to illustrate these points. Decreased respiratory compliance increases tidal Pdi, with Pdimax being reduced by muscle weakness, both favouring the development of respiratory muscle fatigue. An increase in respiratory rate due to pyrexia, or compensation against hypercapnia will increase the tI/$t$tot ratio, again predisposing to fatigue [32]. The normal response to hypercapnia is to increase V'E; patients with NMDs also increase V'E, but they do so by increasing the respiratory rate rather than the tidal volume, unlike normal controls [33]. In addition to muscle fatigue, central respiratory drive has been demonstrated to be reduced in acute hypercapnic failure in NMD patients [34, 35]. Without an adequate compensatory response to the hypercapnia, these patients will develop worsening respiratory failure, leading to acute presentation.

It is outside the scope of this chapter to discuss the respiratory management of chronic NMDs in detail; however, some important management concepts will be highlighted. In chronic NMDs, the slow progressive reduction in respiratory muscle function will cause nocturnal hypoventilation and recurrent infections. The advent of sleep-disordered breathing predates the onset of diurnal hypercapnia [36], and its onset can be used to consider initiation of long-term NIV [37], an important step in chronic management [38, 39], which is discussed in detail in a later chapter in this *Monograph* [40]. Other key management tools include nutritional assistance to maintain healthy respiratory muscle and airway clearance techniques, such as manually assisted coughing or mechanical insufflation–exsufflation, to reduce the risk of infections.

Acute NMDs

While motor neuron disease and the muscular dystrophies tend to present with chronic respiratory failure and are invariably progressive with superimposed acute deteriorations, other neuromuscular diseases can present *de novo* with acute respiratory failure (ARF). Those most commonly encountered include Guillain–Barré syndrome and myasthenia gravis.

Guillain–Barré syndrome is an inflammatory polyradiculoneuropathy that causes acutely progressive diffuse weakness and areflexia, by damaging neurons in the peripheral nervous system. It is most commonly precipitated by a respiratory or gastrointestinal illness, which stimulates the production of antibodies that cross-react with specific gangliosides. There are various clinical entities, and the specific target of the antibodies on the neuron will lead to the various entities [41]. Acute inflammatory demyelinating polyneuropathy presents with both sensory and motor weakness, often with cranial nerve involvement, most commonly in Europe and North America. Acute motor axonal neuropathy presents with isolated muscle weakness, more commonly in Asia and in Central and South America. Acute motor and sensory axonal neuropathy presents with severe muscle weakness and sensory loss. Miller Fisher syndrome presents with ataxia, eye muscle weakness and areflexia but no limb weakness [42–44].

Up to 30% of Guillain–Barré syndrome patients will develop respiratory failure [45]. This is primarily due to diaphragmatic failure. Loss of motor nerve output (neural respiratory drive) to the diaphragm and other respiratory muscles causes respiratory pump failure; ventilatory failure ensues, resulting in hypercapnia. Furthermore, the loss of motor nerve stimulus to the respiratory muscles can cause a decline in respiratory muscle capacity, further compromising respiratory function. Significant morbidity and mortality in Guillain–Barré syndrome is associated with respiratory failure and invasive mechanical ventilation [46]. It is important to identify at-risk patients to ensure appropriate monitoring and to prevent delayed intubation and ventilation. Patients with rapid-onset presentation (<7 days), the inability to lift their head from the bed, an ineffective cough or evidence of significant respiratory muscle weakness (vital capacity <60% predicted) are more likely to require ventilatory support and should be closely monitored within critical care [47]. Invasive mechanical ventilation may be required to support patients while disease-modifying treatments (*e.g.* plasma exchange, intravenous immunoglobulin) are given and recovery occurs [48, 49]. Once intubated, significant numbers of patients will require prolonged mechanical ventilation and tracheostomy formation, and frequently need input from specialist weaning centres [50, 51].

Myasthenia gravis is an autoimmune condition causing dysfunction of the neuromuscular junction by generating antibodies against the post-synaptic terminal. Up to 20% of myasthenia patients will suffer from a myasthenia crisis, usually within 12–18 months of diagnosis [52]. Patients suffer from respiratory failure due to muscle weakness, causing respiratory pump failure. Crises tend to involve all respiratory muscles [53], affecting the intercostals first and then sequentially the accessory muscles of respiration and then the diaphragm [54]. Respiratory muscle weakness decreases the respiratory capacity, making adequate ventilation difficult. Crises can also affect upper-airway and bulbar muscles, causing upper-airway collapse [55]. Upper-airway collapse will increase the work of breathing and so increase the load on the system, thereby causing hypercapnic failure. Signs of impending ventilatory failure include the inability to raise the head and paradoxical breathing [55]. Traditional management of a myasthenic crisis involved invasive mechanical ventilation, which often resulted in prolonged ventilation, weaning and tracheostomy formation [56, 57]. Early NIV may have a role in reducing the need for invasive mechanical ventilation and prolonged weaning [58, 59], although no prospective trials have been performed to compare the efficacy of NIV with invasive mechanical ventilation.

Obesity hypoventilation syndrome

OHS is defined as the triad of obesity, daytime hypercapnia and sleep-disordered breathing in the absence of another cause of respiratory failure. The prevalence is unclear but has been reported as 0.15–0.6% in the general population [60]. Among patients referred to a sleep clinic, the prevalence of OHS was considerably higher in women (16%) than in men (5%), and higher in post-menopausal women (21%) than in pre-menopausal women (5%) [61]. OHS is a distinct condition from obstructive sleep apnoea (OSA), although they often coexist, and is associated with higher morbidity [62] and healthcare costs [63]. The prevalence of OSA is between 2% and 7% of the population [64, 65]. In patients with OSA, the prevalence of OHS is reported as 10–38% [66–69], and, conversely, 90% of OHS patients will have OSA [70]. The narrow definition of OHS may be underestimating the prevalence of OHS due to the unreliable nature of daytime hypercapnia as a marker of nocturnal hypoventilation [71]. There are now calls to include a raised serum bicarbonate level as an

alternative to hypercapnia, as a measure of nocturnal hypoventilation, in the diagnostic definition of OHS, which may increase its overall prevalence [72, 73]. OHS is already the most common indication for domiciliary NIV in some countries [74], and given that, by 2025, one in five adults is expected to be obese [75], this suggests that the prevalence of OHS will substantially increase in the coming years. It is thus important to understand the pathophysiology of OHS and to improve ventilation in these patients.

Obesity increases the work of breathing by causing an increase in the resistance of the airway and a decrease in pulmonary compliance. Obese individuals tend to breathe at lower volumes [76]; for every 1 unit increase in BMI, functional residual capacity and expiratory reserve volume fall by 1% [77]. The lower volumes are probably caused by increased load, demonstrated by significantly increased oesophageal and gastric pressure when compared with normal-weight individuals [78]. This results in limited expiratory flow and gas trapping, generating intrinsic PEEP [79], which increases airway resistance. Pulmonary compliance will fall, due to mass loading on the chest wall [80], breathing at lower lung volumes [81] and reduced lung compliance due to increased pulmonary blood volume [82]. The increased work of breathing requires a higher respiratory drive and increased respiratory muscle recruitment. In OHS patients, the respiratory system is unable to match the demand of the work of breathing. This occurs particularly during sleep due to the exaggeration of the normal physiological changes that occur during sleep stage changes [83]. In the supine position, the diaphragm is projected towards the head by central adiposity, increasing the mass loading effect on compliance [76]. In addition, accessory muscles of breathing are atonic in rapid-eye-movement sleep [84, 85], so cannot be used to help the system adapt to the increased requirement. In addition, there is increased oxygen consumption in OHS, which contributes to respiratory muscle fatigue [86].

Obesity also affects respiratory drive, with increased drive to accommodate the increased load on the respiratory system [76]. Obese patients have a higher oxygen consumption and high $V'CO_2$ than non-obese individuals, due to the metabolic activity of the excess fat and the increased work of the supportive tissues [87, 88]. These patients therefore need an increase in $V'E$ to match the increased ventilatory demand. In OHS patients, there is a failure to increase the central respiratory drive to compensate for the added load, demonstrated by an inadequate increase in tidal volume [69, 89] and the ability to voluntarily hyperventilate to eucapnia [90].

OHS patients can be categorised into two groups: those with associated OSA (90%) and those with sleep hypoventilation only (10%) [73, 91, 92]. OSA causes an increase in $PaCO_2$ through a combination of reduced clearance by cessation of ventilation, and increased $V'CO_2$ by continued metabolic production and the increased work of breathing against an occluded airway. In patients without OHS, this increase in $PaCO_2$ is compensated for by an increase in $V'A$ post-apnoea, which aids the clearance of carbon dioxide [93]. This requires an intact ventilatory control system and normal respiratory mechanics [94]. In patients with OHS, the time period between apnoeas tends to be shorter than in OSA patients without OHS [91], which results in inadequate clearance of carbon dioxide and therefore accumulation. This is exacerbated by the altered pulmonary mechanics already described. This hypercapnia during sleep leads to a renal response to increase serum bicarbonate to buffer the carbon dioxide. As this is a slower compensatory mechanism, the build-up of bicarbonate stimulated by nocturnal hypoventilation therefore persists during wakefulness. This metabolic alkalosis blunts the ventilatory response to carbon dioxide in subsequent sleep [95, 96], further exacerbating hypoventilation and worsening carbon dioxide clearance. This leads initially to nocturnal but eventually to daytime hypercapnia [71, 97].

An important complication of OHS is pulmonary hypertension, with a reported prevalence of 43% [98]. Up to 50% of OHS patients present with symptoms of right heart failure, whereas very few patients with OSA only present similarly [99]. In patients presenting with acutely decompensated OHS, pulmonary hypertension contributes significantly to the severity of hypoxia, with the majority of such patients requiring supplementary oxygen [100]. Failure to reverse this supplemental oxygen requirement is a negative prognostic factor, whereas successful correction of nocturnal hypoventilation with NIV results in improved pulmonary hypertension and fewer patients requiring ongoing oxygen supplementation [100, 101].

All of these changes in the respiratory system leave the OHS patient more vulnerable to acute deterioration when the system undergoes further insult, such as with infection or worsening cardiac function. This increases the risk of ARF. The most common cause of ARF in OHS is idiopathic, followed by pneumonia, acute cardiac failure and sepsis [102, 103]. It is always important to seek and treat any underlying cause of decompensation while providing respiratory support in acute obesity-related respiratory failure.

A detailed discussion about the management of OHS is outside the scope of this chapter; however it is important to highlight some key management strategies [104]. While the management of chronic obesity-related respiratory failure remains debated, with evidence supporting both CPAP and NIV, the cornerstone of management during acute decompensation is unequivocally NIV [105]. Treatment of OHS with NIV has been proved to be physiologically effective in improving sleep architecture and sleep-disordered breathing [92, 106], reversing respiratory failure [107, 108] and improving pulmonary function [101, 107, 109], with more limited data suggesting clinical efficacy to reduce healthcare utilisation [63, 108] and mortality [101, 110]. The successful management of patients with chronic respiratory failure plays an important role during acute episodes. A significant number of patients presenting acutely have no identifiable cause for deterioration [103]; these patients are likely to have suboptimal control of their sleep-disordered breathing. Patients presenting with acute *de novo* obesity-related respiratory failure have a lower perceived symptom burden than those who present *via* sleep services, and therefore a high index of suspicion should be maintained and $PaCO_2$ measured in high-risk patients [111]. Furthermore, if patients poorly tolerate NIV at home, they are more likely to fail NIV acutely [103, 112], so it is important to identify these patients and make early decisions on escalation of therapy and then manage them in an appropriate clinical setting with access to rapid endotracheal intubation if needed. The effect of pharmacotherapy in OHS is unclear. Limited studies have been conducted on medroxyprogesterone and acetazolamide, and these should be preserved for uses in specialist centres for treatment-resistant cases [113].

Other causes of hypoventilation

Cystic fibrosis

Although cystic fibrosis is usually associated with type I respiratory failure, in its advanced stages, hypercapnia can develop and is associated with poor outcomes [114, 115]. Management tends to be with invasive mechanical ventilation [115]; however, some evidence reports the value of NIV in these patients [116, 117]. There are increasing reports of its use as a bridge to support the patient until transplantation [117–119]. As with

COPD, respiratory failure is the result of a significant load on the respiratory system, which, even with a compensatory elevated drive, cannot maintain eucapnia.

Chest wall disorders

Isolated chest wall disorders, such as kyphoscoliosis, ankylosing spondylitis and pectus excavatum, can all cause hypercapnia due to hypoventilation. They cause a decrease in respiratory system compliance by increasing stiffness of the system [120], causing a decrease in lung volumes and worsening pulmonary mechanics by moving the respiratory system to an inefficient portion of the pressure–volume curve [121]. This leads to alveolar hypoventilation and hypercapnia. The increased work of breathing that this causes will increase oxygen consumption in the inspiratory muscles, causing muscle fatigue and further exacerbating the respiratory pump failure.

Conclusion

A number of pathological entities produce hypercapnic respiratory failure. These disorders produce ventilatory failure *via* disruption of the respiratory muscle load–capacity–drive relationship. While COPD is the commonest cause encountered in clinical practice, a number of other important conditions will frequently present to critical care or pulmonary physicians. The two largest groups are obesity-related respiratory failure and neuromuscular-related respiratory failure. Both of these clinical groups can complicate respiratory failure acutely or present as acute decompensation of chronic respiratory failure. In both circumstances, it is important to evaluate the patient comprehensively for an underlying precipitant, for example pneumonia or heart failure, and treat this appropriately. An understanding of the mechanism of respiratory failure allows appropriate ventilatory support to be instigated. In the majority of cases, this will be *via* NIV, but a cohort of patients will require transition to invasive mechanical ventilation, and appropriate physiological monitoring of patients and the use of clinical predictors of failure of NIV are important in the acute management.

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Chapter 7

Severe community-acquired pneumonia

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Severe community-acquired pneumonia (sCAP) is the most frequent infectious cause of admission to the ICU and is associated with a high mortality rate that can reach 30–50%. Severity assessment is a main point of sCAP management to ensure the appropriate site of care and antibiotic therapy. The microbial aetiology of sCAP has changed over time; *Streptococcus pneumoniae* (pneumococcus) is the most frequent pathogen, and the proportion of sCAP caused by respiratory viruses and with a polymicrobial aetiology has increased, mainly due to better detection with new molecular techniques. Antibiotic therapy is a key factor in the management of sCAP, and several studies have shown that early empirical antibiotic administration improves patient outcomes. In general, the management of sCAP includes microbiological diagnosis, severity assessment and early empirical antibiotic treatment. The main challenge is the high prevalence of multidrug-resistant pathogens worldwide. This chapter focuses on the current state of knowledge on the management of sCAP.

Community-acquired pneumonia (CAP) represents a public health problem of substantial magnitude, with an annual incidence ranging from 1.6 to 10.6 per 1000 adult population in Europe [1]. The incidence of CAP increases considerably with age and has a wide spectrum of clinical severity, from self-limiting disease to septic shock and ARDS [2]. The term severe CAP (sCAP) identifies patients who require ICU admission and higher levels of care, such as mechanical ventilation and vasopressor support [3, 4]. Transfer to the ICU for delayed respiratory failure or delayed onset of septic shock is associated with a 2- to 2.6-fold increase in the risk of hospital mortality [3, 5]. Despite advances in antimicrobial therapy and supportive measures, mortality in patients with sCAP remains high, ranging from 31% to 58% [6–9]. However, there are conflicting data regarding whether these rates are increasing over time [10, 11].

This chapter provides an overview of the current data on sCAP in immunocompetent patients, including its epidemiology, microbial aetiology, antimicrobial therapy and management. We discuss the major studies on sCAP.

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Epidemiology

The Genetic and Inflammatory Markers of Sepsis (GenIMS) study group examined a population of 1895 CAP patients, of which 302 patients were admitted to the ICU, with 17.3% hospital mortality [6]. It is well recognised that there is also an increased rate of death in CAP patients in the months following discharge [12], and in patients with sepsis, there is significant excess mortality for at least 5 years [13]. The Genetics of Sepsis in Europe (GenOSept) study, which analysed 1166 patients with sCAP admitted to the ICU, reported the following mortality rates: 17% at 28 days, 19% at intensive care discharge, 24% at hospital discharge and 27% at 6 months [14].

However, there is reason to believe that outcomes for sCAP are improving with implementation of the Surviving Sepsis Campaign (SSC) guidelines [15] and CAP guidelines [3], a greater awareness of the importance of therapy timing and the use of new diagnostic microbiology tests [16]. Gattarello *et al.* [17], in a case–control study of the outcomes of 160 patients with non-*Streptococcus pneumoniae* (nonpneumococcal) CAP in the ICU over two time periods (2000–2002 and 2008–2013), reported that the latter group had improved ICU survival (34.7% *versus* 16.7%; p=0.002) and had more patients receiving combined and early antimicrobial therapy within 3 h (76.4 *versus* 90.3% and 37.5 *versus* 63.9%, respectively; p<0.05). In the case of pneumococcal sCAP, the study by Mongardon *et al.* [18] analysed 222 cases and found that, although antibiotic therapy was adequate in 92.3% of cases, hospital mortality reached 28.8%. The study concluded that, in the ICU, mortality for pneumococcal CAP remains high, despite adequate antimicrobial treatment.

Pathophysiology of pneumonia

Pneumonia is an infectious process resulting from the invasion and overgrowth of pathogenic micro-organisms in lung parenchyma, the breakdown of respiratory tract defence mechanisms and the production of intra-alveolar exudates [19]. The development of pneumonia and its severity are influenced by the balance between pathogen factors (*e.g.* virulence and inoculum size) and host factors (*e.g.* loss of protective upper airway reflexes allowing aspiration of contents from the upper airways into the lung). The inflammatory cascade triggers an exuberant immune response in the lungs in response to infection and the leakage of plasma into the alveoli and loss of surfactant, resulting in air loss and consolidation. The patient breathes faster and faster in an effort to inhale more oxygen and remove more carbon dioxide. sCAP cases with hypoxia or hypercapnia generally require intubation and mechanical ventilation.

Clinical presentation and primary investigations

Diagnosis of sCAP includes clinical criteria, radiographic examination and diagnostic testing for microbial aetiology. The most frequent symptoms in sCAP include cough, fever, dyspnoea, pleuritic chest pain and sputum production. Mental confusion and gastrointestinal symptoms will also be present in some cases [3].

Clinicians should take into consideration risk factors such as age, which is an important risk factor for the development of sCAP, and comorbidities (*e.g.* COPD, diabetes mellitus, chronic renal failure) that may affect the severity of pneumonia.

Primary investigations include blood tests that provide information about the inflammatory state (*e.g.* C-reactive protein (CRP), leukocyte cell count), associated organ failure (*i.e.* acute renal failure) and the severity of the disease. Biomarkers are another important test that can help clinicians distinguish bacterial pneumonia from other disorders such as congestive heart failure in elderly patients presenting with respiratory symptoms and suspicion of pneumonia (frequent entities such as chronic cardiovascular disease are a common comorbidity in this population) [20].

According to CAP management guidelines [3, 4, 21], blood cultures, sputum Gram stains and cultures, urinary antigen tests for pneumococcus and *Legionella pneumophila*, and invasive respiratory tract sample cultures should be carried out in sCAP cases.

If the patient is intubated, bronchoscopy using BAL or a protected specimen brush are alternative invasive methods for aetiological diagnosis (*e.g.* resistant micro-organisms, polymicrobial infections, unusual pathogens). For quantitative cultures of endotracheal aspirate samples, a threshold of $>10^5$ CFU·mL^{-1} is used to distinguish colonisation from infection [22].

Risk factors and genetics

Some individuals are more prone to pneumonia than others due to both intrinsic and extrinsic factors, and recent data have revealed a role of individual genetic variability in predisposition to the development of pneumonia and its clinical presentation [2]. For example, specific variants of the *FER* gene are associated with a reduced risk of death in patients with sepsis due to pneumonia [23]. Therefore, the *FER* gene may be a potential target for new therapies. Misch *et al.* [24] showed that a single-nucleotide polymorphism in a Toll-like receptor, specifically the Toll-like receptor 6 polymorphism T359C, is associated with increased risk of Legionnaires' disease.

Assessment of severity

Many studies of the epidemiology of patients with CAP have demonstrated the importance of assessing the severity of illness and stratifying patients on the basis of their risk of mortality The most firmly established prediction scores, as determined by the Pneumonia Severity Index (PSI) [25] and CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age $\geqslant$65 years) test [26], do not have sufficient operating characteristics to be useful for making ICU triage decisions in sCAP. Unfortunately, the use of mortality as the definition of CAP severity is often clouded by questions of limitations of care in patients of advanced age and the influence of comorbidities.

In 2007, the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) issued guidelines [3] on the management of CAP, including specific criteria to identify patients for ICU admission. These guidelines recommended that the presence of one of the major or three or more of the nine minor criteria should indicate ICU admission (table 1). The major criteria represent the stronger indicators for sCAP and comprise the need for mechanical ventilation or vasopressors (or both). The IDSA/ATS criteria have now been validated for prediction of 30-day mortality and ICU admission in several countries [27–29]. However, individual studies have argued that the minor criteria are of unequal weight; for example, in our study published in 2009 [29], we found that

Table 1. Criteria for ICU admission in severe community-acquired pneumonia

Major criteria
- Invasive mechanical ventilation
- Septic shock with need for vasopressors

Minor criteria
- Blood urea nitrogen level $\geqslant$20 mg·dL^{-1} (7.14 mmol·L^{-1})
- Confusion/disorientation
- Hypotension requiring aggressive fluid resuscitation
- Hypothermia: core temperature <96.8°F (36°C)
- Leukopenia: WBCs <4000 cells·mm^{-3} (4×10^{9} cells·L^{-1})
- Multilobar infiltrates
- P_{aO_2}/F_{IO_2} ratio $\leqslant$250 mmHg
- Respiratory rate $\geqslant$30 breaths·min^{-1}
- Thrombocytopenia: <100×10^{3} PLTs·mm^{-3} (100×10^{9} PLTs·L^{-1})

WBC: white blood cell; PLT: platelet. Reproduced and modified from [3] with permission.

mental confusion and leukopenia had the strongest association with mortality. Thus, the need for ICU admission derived from minor severity criteria alone is uncertain.

Other new models specific to sCAP, which focus on the early detection of respiratory and circulatory failure rather than on age and underlying illnesses, have been developed, including an Australian model called SMART-COP (low systolic blood pressure, multilobar chest radiography involvement, low albumin level, high respiratory rate, tachycardia, confusion, poor oxygenation and low arterial pH) [30] and a Spanish model called CURXO-80 (altered mental status, blood urea nitrogen >30 mg·dL^{-1}, respiratory rate >30 breaths·min^{-1}, systolic blood pressure <90 mmHg, arterial pH <7.30, multilobar/bilateral lung affectation, oxygen arterial pressure <54 mmHg or ratio of arterial oxygen tension to fraction of inspired oxygen <250 mmHg and age >80 years) [31]. These scores incorporate variations of the ATS minor criteria and/or additional factors such as low arterial pH, albumin, tachycardia and hyponatraemia. S_{pO_2} and arterial blood gas analysis can give important information about severity (*e.g.* S_{pO_2} <92% can be considered a safer cut-off than S_{pO_2} <90% for hospital admission); S_{pO_2} is therefore a criterion in these scores.

Clinical high-risk identification should focus on acute respiratory or extrapulmonary sepsis, or comorbidity-associated organ dysfunction, and careful clinical evaluation should be complemented by regular assessment of abnormal vital signs and the minor criteria during the first days of hospitalisation. This strategy must be supplemented by the continuous evaluation of individual treatment goals.

Biomarkers

The role of biomarkers in the inflammatory response and their association with diagnosis, severity of the infection and treatment management continue to be subjects of growing interest. Procalcitonin (PCT) has high sensitivity but moderate specificity in differentiating between bacterial and viral infections [32, 33]. In the most comprehensive study on the prognostic properties of CAP, including new biomarkers (*e.g.* mid-regional pro-adrenomedullin (MR-proADM), mid-regional pro-atrial natriuretic peptide, pro-arginine-vasopressin (copeptin), C-terminal proendothelin-1) and biomarkers already in use (*e.g.* PCT, CRP, white blood cell

count and CRB-65 score (CURB-65 without urea)), MR-proADM showed the best individual performance, and a combination of CRB-65 with MR-proADM showed the best overall prognostic performance [34, 35].

The main advantage of PCT over CRP in CAP diagnosis lies in its faster kinetics. Studies suggest that PCT levels on admission can identify the severe outcomes of CAP and add to the prognostic properties of clinical risk scores [34].

Schuetz *et al.* [34], in a two-centre, retrospective derivation–validation study of septic patients, found that a 72-h PCT decrease of >80% had a negative predictive value of around 90%; this may help to identify individuals with a reduced risk of mortality, who are therefore good candidates for early discharge from the ICU. However, false-negative levels of PCT in patients with severe sepsis or even septic shock have been reported [36]. Despite this, the presence of CRP and the speed with which it decreases during the first week of therapy have been found to correlate with prognosis in ICU patients with severe pneumonia [37].

In the field of therapy, evolving data on PCT suggest its potential utility in deciding the duration of antibiotic therapy. Thus, low PCT levels in the course of pneumonia have been shown to shorten the duration of antibiotic treatment without compromising patient safety in a variety of interventional trials and even in an ICU setting [38, 39].

Currently, all these markers are limited by absent rapid or even on-site availability and high costs. Furthermore, the cut-off points for all biomarkers for different clinical settings still have to be confirmed by large interventional trials [40].

Microbial aetiology

The spectrum of causal pathogens in sCAP is broader than that in nonsevere cases [41]. The gold standard diagnostic techniques used to identify bacteria causing respiratory tract infections remain the Gram stain and semi-quantitative conventional culture from direct respiratory samples, followed by bacterial identification, currently using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry, and susceptibility testing of the potential pathogen [42–44]. In addition to the difficulty of differentiating between colonisation and infection, this process requires a minimum of 2 days and has low sensitivity, especially if the sample is taken after the start of antibiotic treatment [45]. As a consequence, many patients receive inappropriate antibiotic treatment, which may increase morbidity and mortality [46–48]. Development of molecular techniques, especially real-time PCR, has contributed to the recognition of the real incidence of respiratory viruses and polymicrobial infection in sCAP. One of the advantages of molecular diagnostics is the ability to identify pathogens in patients already receiving antibiotic treatment. Thus, these techniques can increase the rate of microbiological findings of respiratory pathogens in pneumonia from 39% using culture-based methods to 87% of cases using these new techniques, as shown in a recent study [49].

The pathogens that cause sCAP can vary according to geographical area and underlying risk factors. *Streptococcus pneumoniae* is still the leading pathogen, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, *Legionella pneumophila*, *Enterobacteriaceae* (especially *Escherichia coli* and *Klebsiella* spp.) and *Pseudomonas aeruginosa* (figure 1) [50–52].

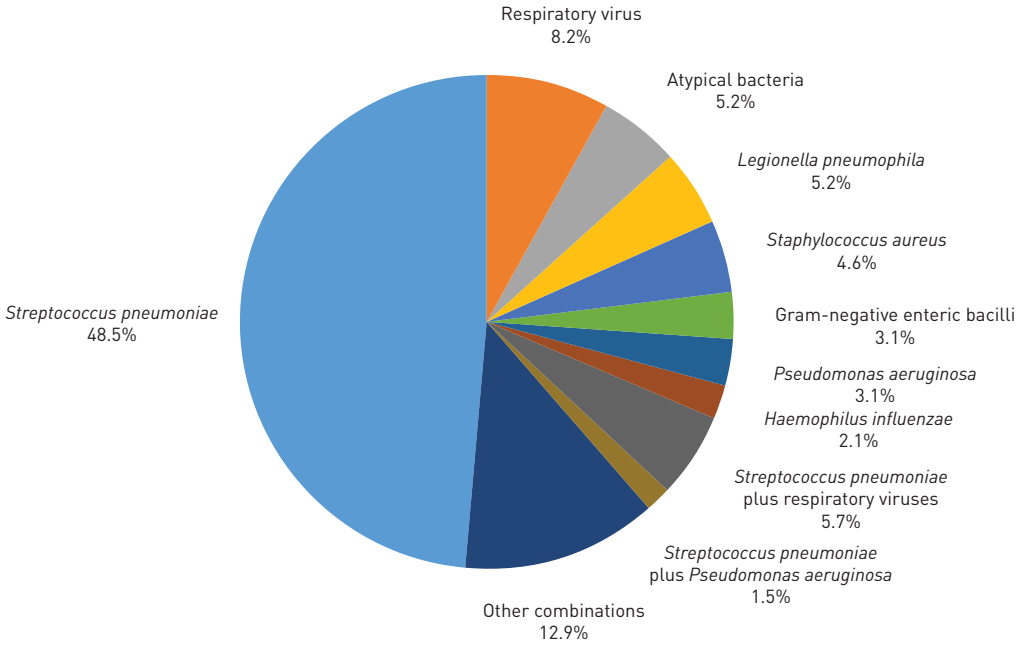

Figure 1. Microbial aetiology distribution of pathogens in severe community-acquired pneumonia. Data from [50].

The most common blood isolate in patients with CAP is *S. pneumoniae*, which is also reported to be common in patients with severe sepsis. It has been found to trigger bacteraemia and sepsis in mouse lung infection models [53].

In a study by Cilloniz *et al.* [41] in patients with CAP admitted to the ICU, the most common aetiologies were *S. pneumoniae* (42%), polymicrobial aetiology (22%) and atypical pathogens (18%). *S. pneumoniae* infection resulted in the highest number of deaths, although the relative mortality rates were higher for *S. aureus*, Gram-negative enterobacteria, *P. aeruginosa* and polymicrobial aetiologies.

Regarding respiratory viruses, a study from the USA investigating the aetiology in patients with sCAP admitted to ICU found that the most frequently reported viruses were influenza virus (9.7%), rhinovirus (8.4%) and metapneumovirus (3.3%) [54].

Bacteraemia is more common than respiratory virus infections in sCAP, and up to 20% of sCAP episodes are caused by polymicrobial infection [55]. An interesting study carried out in Japan on 1032 patients with CAP found that polymicrobial infection was confirmed in 9.2% of all cases, 18% in sCAP and 12.5% in the group of nonsurvivors, and that polymicrobial infection was a risk factor for the severity of CAP [56]. A study by Cilloniz *et al.* [50] found that 11% of 362 ICU patients with CAP had a polymicrobial infection, and the predictors of polymicrobial aetiology were chronic respiratory disease and ARDS criteria on admission.

Respiratory viruses are the micro-organisms most frequently associated with a polymicrobial aetiology. Polymicrobial infection involving influenza virus A and *S. aureus* is one of the main causes of sCAP [57]. Aspiration pneumonia is a common cause of sCAP and is generally polymicrobial, with both Gram-positive and Gram-negative anaerobes [58].

Multidrug-resistant organisms in sCAP

Multidrug-resistant (MDR) organisms that cause CAP represent an emerging problem because of the increasing number of residents living in healthcare facilities and others receiving immunosuppressant therapy because of cancer or transplantation. The most common MDRs in sCAP are *P. aeruginosa*, *Enterobacteriaceae* positive for extended-spectrum β-lactamase and methicillin-resistant *S. aureus* (MRSA) (collectively referred to as PES) [59]. Although the prevalence of MDR pneumonia is still low in Europe (7.6% in Spain and 3% in UK, with the most common organism found being MRSA), this represents patients requiring ICU admission, with unfavourable outcomes [60].

In an attempt to evaluate risk factors for acquiring MDR bacteria in CAP, Aliberti *et al.* [61] found that hospitalisation in the preceding 90 days (OR 4.87, 95% CI 1.90–12.4; p<0.001) and residency in a nursing home (OR 3.55, 95% CI 1.12–11.24; p<0.031) were independent predictors for an actual infection with a resistant pathogen.

Shorr *et al.* [62] developed a simple risk score that appears valid for assessing the probability of an MRD organism in patients hospitalised initially with CAP. The criteria are as follows: recent hospitalisation, living in a long-term care facility, chronic haemodialysis and ICU admission within 24 h of evaluation in the emergency department, with an area under the receiver operating characteristic curve (AUROC) for the risk score of 0.71; the AUROC for healthcare-associated CAP was 0.62. After validating the score in a later study by Aliberti *et al.* [63], the authors concluded that the application of risk scores in clinical practice makes it possible predict the presence of MDR pneumonia. A study by Prina *et al.* [59], which analysed 1519 patients with CAP who presented aetiological diagnosis, found that PES pathogens were identified in 6% of the CAP cases; the study also found that PES pathogens are associated with increased risk of 30-day mortality (OR 2.51, 95% CI 1.20–5.25; p=0.015).

Further studies are needed to evaluate these scores and to identify patients with MDR sCAP as early as possible.

Therapy

The initial treatment of sCAP requires complex management involving multiple tasks: respiratory support, monitoring, haemodynamic assessment and antimicrobial therapy (figure 2).

Antimicrobial therapy

Antibiotic treatment for sCAP remains largely empirical; it should be started as soon as cultures have been taken, with a broad-spectrum regimen, without waiting for the results to be reported.

The importance of guideline-concordant therapy remains a main factor to improve clinical outcomes in sCAP, as indicated by subanalysis of the Community-Acquired Pneumonia in Intensive Care Study (CAPUCI) study [64].

The goal of appropriate antimicrobial treatment therefore is to maximally reduce or eradicate the bacterial load in order to achieve clinical success and minimise the potential for

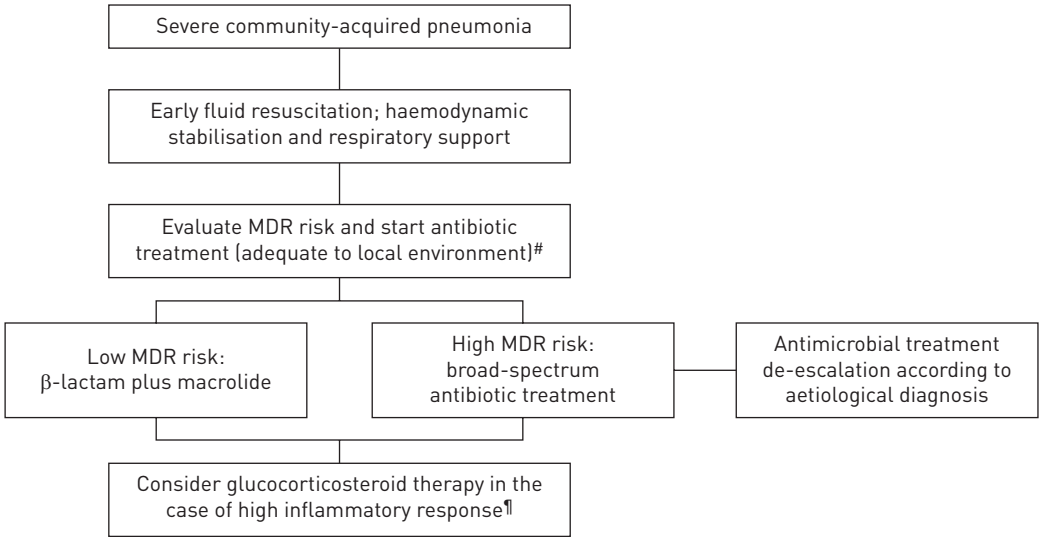
Severe community-acquired pneumonia
Early fluid resuscitation; haemodynamic stabilisation and respiratory support
Evaluate MDR risk and start antibiotic treatment (adequate to local environment)#
Low MDR risk: β-lactam plus macrolide
High MDR risk: broad-spectrum antibiotic treatment
Antimicrobial treatment de-escalation according to aetiological diagnosis
Consider glucocorticosteroid therapy in the case of high inflammatory response¶

Figure 2. Initial management of severe community-acquired pneumonia. MDR: multidrug-resistant. #: consider antimicrobial treatment according to the recommendations in table 2; ¶: a high inflammatory response is defined as a level of C-reactive protein >150 mg·mL^{-1}.

development of resistance. Specific risk factors, such as comorbidities (*e.g.* COPD, bronchiectasis) or previous hospitalisation, should be taken into account on an individual basis.

Patients with septic shock

In patients with septic shock, treatment must not be delayed for >1 h after diagnosis [3, 65]. A multicentre study by Kumar *et al.* [47] of 2154 septic shock patients showed that effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge.

In patients with septic shock, resuscitation requires the use of intravenous fluids and vasopressors, oxygen therapy and mechanical ventilation provided as necessary. The European Society of Intensive Care Medicine also advocates the measurement of lactate concentrations after adequate fluid resuscitation until they return to a normal level (<2 mmol·L^{-1}) [66]. There is evidence, however, that a mean arterial pressure (MAP) of around 65 mmHg is sufficient in most patients with septic shock, although in patients with a history of hypertension, a higher MAP is associated with a lower risk of acute kidney injury [66]. Vasopressors may have to be used if fluid resuscitation is not sufficient, or may be indicated to maintain the desired value of MAP. A major concern in patients with sepsis due to pneumonia is the risk associated with cumulative fluid balance and blood transfusion because of worsening respiratory function [67].

sCAP

The most consistent data come from studies of sCAP, where guideline adherence is associated with reduced mortality [68, 69]. In a study by Bodi *et al.* [68], which included 529 patients with sCAP, significantly higher mortality was documented among patients with nonadherence to treatment guidelines (33.2% *versus* 24.2%).

According to the guidelines for management of CAP in Europe and the USA [3, 4], therapy for sCAP depends on the presence of risk factors for *P. aeruginosa* infection. These are chronic or prolonged use of broad-spectrum antibiotic therapy, structural lung disease (bronchiectasis), repeated exacerbations of COPD, corticosteroid therapy, malnutrition, and HIV infection and other forms of immunosuppression [3, 4]. In a recent study by Cilloniz *et al.* [52] on CAP due to *P. aeruginosa*, the authors reported that male sex, chronic respiratory disease, CRP <12.35 $mg \cdot dL^{-1}$ and PSI risk class IV–V were independently associated with *P. aeruginosa* CAP, whereas prior antibiotic treatment was the only risk factor for MDR *P. aeruginosa* CAP. In the analysis of 30-day mortality for this CAP population, CAP due to *P. aeruginosa* was one of the risk factors [52].

For treatment of sCAP in patients without pseudomonal risk, an intravenous β-lactam (usually cephalosporin III) plus either a macrolide or respiratory fluoroquinolone is recommended. In patients with risk factors for pseudomonal infection, an antipseudomonal β-lactam should be combined with either levofloxacin or ciprofloxacin, or the antipseudomonal β-lactam can be combined with an aminoglycoside and azithromycin (table 2) [4].

In cases of suspected community-acquired MRSA infection (*e.g.* prior influenza-like illness, necrotising severe pneumonia), the guidelines recommend adding vancomycin or linezolid to the other recommended agents [3].

Anaerobic coverage with a combination of a cephalosporin and clindamycin is indicated only in patients with a risk of aspiration, such as those suffering from alcoholism, loss of consciousness, neurological disease or dysphagia due to mechanical or neurological upper digestive tract dysfunction.

The implementation of early (<2 days) antiviral therapy was found to be associated with lower mortality in ventilated patients with pneumonia caused by the 2009 H1N1 strain of influenza virus [3, 70]. The neuraminidase inhibitors oseltamivir and zanamivir can be used for pneumonia caused by influenza viruses and reduce the duration of symptoms, risk of hospitalisation and complications [70]. In addition to antiviral agents, antibacterial agents targeting *S. pneumoniae* and *S. aureus* are also necessary [50].

Table 2. Therapy for severe community-acquired pneumonia following clinical assessment

No risk factors for *Pseudomonas aeruginosa*
- Nonantipseudomonal cephalosporin III+macrolide
- or
- Moxifloxacin or levofloxacin±nonantipseudomonal cephalosporin III

Risk factors for *Pseudomonas aeruginosa* [#]
- Antipseudomonal cephalosporin[¶] or acyl ureidopenicillin/β-lactamase inhibitor or carbapenem (meropenem preferred, up to 6 g possible, 3 g twice a day in 3 h infusion)
- Plus ciprofloxacin[+]
- or
- Plus macrolide+aminoglycoside (gentamycin, tobramycin, amikacin)

[#]: risk factors include: 1) recent hospitalisation (in last 3 months), 2) frequent (>4 courses·$year^{-1}$) or recent administration of antibiotics (in last 3 months), 3) severe disease (FEV_1 <30% in last 3 months) and 4) oral steroid use (>10 mg prednisolone daily in the last 2 weeks); [¶]: ceftazidime plus penicillin G for coverage of *Streptococcus pneumoniae*; [+]: levofloxacin 750 mg over 24 h or 500 mg twice a day is an alternative. Reproduced and modified from [4] with permission.

As soon as the causative pathogen has been identified, de-escalation should be performed by selecting the most appropriate antimicrobial agent that covers the pathogen. De-escalation of initial broad-spectrum therapy to a narrow-spectrum agent may prevent the emergence of resistant organisms, minimise the risk of drug toxicity and reduce costs.

Combination antibiotic therapy

Data regarding the use of combination therapy are limited to a few RCTs, and most of the data come from observational studies that have evaluated the benefit of using combination antibiotic therapy *versus* monotherapy in patients with sCAP who were admitted to the ICU. The most thoroughly investigated combination is macrolide combination therapy, which is associated with lower mortality compared with a quinolone combination, a consistent finding in almost all large databases of patients with sCAP [71–73]. A study by Waterer *et al.* [74] showed that mortality associated with pneumococcal pneumonia was reduced when patients were treated empirically with combined antibiotic therapy including a macrolide. Rodriguez *et al.* [71], in the CAPUCI study, found that, in the subset of ICU patients who had CAP and septic shock, combination antibiotic therapy improved survival rates (OR 1.69, 95% CI 1.09–2.60; p=0.01). Similarly, only patients with sCAP and septic shock who were treated with combination antibiotic therapy (58% with a third-generation cephalosporin plus a macrolide), compared with those treated with monotherapy (42% fluoroquinolone), had a higher 28-day in-ICU survival rate (hazard ratio (HR) 2.69, 95% CI 1.09–2.60) [73]. Conclusively, in a meta-analysis including 28 observational studies of almost 10 000 critically ill patients with CAP, macrolide use was associated with a significant 18% relative (3% absolute) reduction in mortality compared with nonmacrolide therapies [75]. However, in a study by Garin *et al.* [76], in Switzerland, patients infected with atypical pathogens (HR 0.33, 95% CI 0.13–0.85) or with PSI category IV pneumonia (HR 0.81, 95% CI 0.59–1.10) were less likely to reach clinical stability with monotherapy compared with combination therapy (β-lactam plus a macrolide).

From the above-mentioned data, it has become increasingly clear that the benefit of combination therapy in sCAP is seen only when a macrolide is part of the regimen, especially in pneumococcal bacteraemia [77, 78]. The benefit of a macrolide may also explain the finding of greater clinical relapse in patients randomised to a β-lactam alone if their streptococcal urinary antigen was positive [79]. The benefit also extends to patients infected with macrolide-resistant pathogens (*e.g.* macrolide-resistant pneumococcal infections, and even cases of Gram-negative infections) [72]. Clearly, the immunomodulatory effects of macrolides may have an important effect on mortality in CAP, but these drugs also have direct effects on bacteria by inhibiting quorum sensing [80]. Thus, for intubated patients, macrolides have been shown to inhibit biofilm formation and decrease mucus hypersecretion, leading to improved mucociliary clearance. However, the cardiotoxicity of macrolides has been linked recently to a slight increase in mortality. The study by Schembri *et al.* [81] is currently the only study that has looked specifically at protocol-defined CAP and showed an increased risk of long-term cardiac events. However, Mortensen *et al.* [82] showed that the benefit of azithromycin in reducing CAP mortality outweighed the risk of cardiotoxicity.

The SSC guidelines recommend antibiotic therapy for 7–10 days [65]. Longer treatments are suggested for slow responses, nondrainable foci, *S. aureus* bacteraemia, some fungal or viral infections, and immunological deficiencies such as neutropenia [65]. These guidelines

now also include the use of biomarkers, especially PCT, which can be used to assist in decisions regarding the discontinuation of empirical antibiotics (grade 2C) and when considering the diagnosis of candidiasis [65]. The largest RCT published to date reported that a PCT-guided strategy to treat suspected bacterial infections in nonsurgical patients may reduce antibiotic exposure [38].

Recently, a multicentre observational study by MILLER *et al.* [83] reported that, after implementing a resuscitation bundle, hospital mortality for severe sepsis and septic shock declined from 21.2% to 8.7% over 7 years. Better compliance with resuscitation bundles reduced the subsequent need for support for another organ.

Adjunctive therapies

Corticosteroids

The relationship between low-dose corticosteroid use and mortality in patients with sCAP remains unclear. Corticosteroids may be used in patients with sCAP because they are the most powerful inhibitors of inflammation and can potentially decrease the development of ARDS, sepsis and mortality. In a recent study from Japan of 6925 patients with sCAP in the ICU, the authors concluded that low-dose corticosteroid use may be associated with reduced 28-day mortality in patients with CAP complicated by septic shock [84].

Recently, TORRES *et al.* [85] performed an RCT comparing methylprednisolone (0.5 $mg \cdot kg^{-1}$ twice daily for 5 days) *versus* placebo in patients with sCAP according to ATS or PSI risk class V and with a high systemic inflammatory response (CRP >15 $mg \cdot dL^{-1}$). They found that corticosteroids reduced the risk of treatment failure, with an OR of 0.34 (95% CI 0.14–0.87). This reduction in treatment failure was more evident in late treatment failure (3% *versus* 25%; p=0.001), and especially in radiographic progression (2% *versus* 15%; p=0.007). In another RCT by BLUM *et al.* [86], a total of 785 patients with CAP were randomised to receive oral corticosteroids (50 mg prednisone for 7 days) or placebo as adjunctive treatment. The corticosteroid group reported a shorter time to reach clinical stability in comparison with the placebo group (3 days *versus* 4.4 days; p<0.001), with no increase in complications. Additionally, NIE *et al.* [87], in a meta-analysis, concluded that corticosteroids produced a benefit in terms of reduction of ARDS, length of hospital and ICU stay, duration of intravenous antibiotics and time to clinical stability, without a significant increase in side-effects.

The potential side-effects from corticosteroids in CAP should be mentioned. Theoretically, corticosteroids may favour the onset of metabolic disorders, such as hyperglycaemia, gastroduodenal bleeding, osteonecrosis, muscle weakness, psychotic reactions and superinfection [88]. In most of the studies, hyperglycaemia occurred frequently in patients treated with corticosteroids. However, for influenza sCAP, the results of a Cochrane meta-analysis suggested that corticosteroids should not be used as an adjunctive treatment, as they were associated with increased mortality [89].

High-flow oxygen therapy

High-flow oxygen therapy is the first approach for the management of hypoxaemic respiratory failure and may also decrease the need for tracheal intubation in patients with

Table 3. Advisory Committee on Immunization Practices (ACIP) 2015 recommendations for PCV13 and PPV23

Pneumococcal vaccine in naïve persons ⩾65 years of age
Naïve persons should receive a single dose of PCV13 first, followed by a dose of PPV23 ⩾1 year later.
Prior vaccination with PPV23 at ⩾65 years of age
Adults ⩾65 years of age who have previously received one or more doses of PPV23 should also receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given ⩾1 year after receipt of the most recent PPV23 dose. In the case of patients who need repeated PPV23, the period between received PCV13 and the new dose of PPV23 should be ⩾1 year, and 5 years after the most recent dose of PPV23.
Immunocompromised patients
The ACIP recommendations for immunocompromised patients remain unchanged [92].
Routine PCV13 use among adults ⩾65 years of age
The recommendations for routine PCV13 use among adults ⩾65 years of age will be re-evaluated in 2018 and revised as needed.

PCV13: pneumococcal conjugate vaccine protecting against 13 types of pneumococcal bacteria; PPV23: pneumococcal polysaccharide vaccine protecting against 23 types of pneumococcal bacteria. Data from [93, 94].

sCAP. Several studies have indicated that NIV may also work in patients with sCAP, particularly in patients with COPD [1]. A meta-analysis suggested that the appropriate use of NIV in pneumonia can reduce the need for endotracheal intubation (OR 0.28, 95% CI 0.09–0.88), ICU mortality (OR 0.26, 95% CI 0.11–0.61) and the length of stay in ICUs (mean OR −1.00, 95% CI −2.05 to −0.05) [90]. NIV has been shown to reduce intubation in patients with ARDS in 54% of treated cases [91]. However, use of high-flow nasal cannulae and NIV must not delay endotracheal intubation when needed. Among patients in a French study who were intubated after failure of NIV for severe CAP, those with a longer delay in intubation were more likely to die [91]. For mechanically ventilated patients, protective ventilation is strongly recommended on diagnosis of ARDS.

Prevention

The most important specific measure to prevent pneumonia is the use of pneumococcal vaccines (polysaccharide and conjugated) and influenza vaccines in all adults >65 years of age and for younger people with medical conditions that place them at a high risk of pneumonia morbidity and mortality. The Advisory Committee on Immunization Practices 2015 recommendations for vaccination are given in table 3.

Conclusions

Despite the improvement in microbial diagnosis, antibiotic therapy and clinical management, overall mortality remains high in patients who present with sCAP. Clinicians in emergency departments should pay attention to early diagnosis of sCAP cases in order to decide on early ICU admission, microbial diagnosis and appropriate antibiotic therapy selection to prevent patient deterioration.

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Chapter 8

Acute exacerbations of interstitial lung disease

Marcel Veltkamp[1] and Jan C. Grutters[1,2]

Interstitial lung diseases (ILDs), or diffuse parenchymal lung disorders, constitute a group of more than 150 different disorders characterised by inflammation of the lung parenchyma or interstitium, sometimes followed by the occurrence of pulmonary fibrosis. In the most frequently occurring interstitial disorders, such as sarcoidosis, idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, hypersensitivity pneumonitis and collagen vascular disease-related interstitial pneumonias, acute worsening of pulmonary symptoms can occur that can be defined as an acute exacerbation. There are important differences in presentation, aetiology and prognosis of acute exacerbations between these different ILDs. In sarcoidosis, an acute exacerbation is defined as an increase of pulmonary symptoms caused by new or worsening granulomatous inflammation. In acute exacerbations of IPF, for example, an acute worsening has to be present with new ground-glass abnormalities on CT and can be provoked by multiple triggers, such as infection, mechanical ventilation, drug toxicity and aspiration. When an acute exacerbation occurs in sarcoidosis, starting or increasing the dose of prednisolone is often successful. Steroids are also often used in treating an acute exacerbation of IPF, although unfortunately with a much lower chance of success. In acute exacerbations of non-IPF pulmonary fibrosis there might be an even more logical rationale for increasing the amount of immune suppression. However, in line with IPF, strong evidence is also lacking, indicating the need for future studies addressing this issue. Best supportive care during acute exacerbations, such as mechanical ventilation, is challenging and should be discussed case by case.

Interstitial lung diseases (ILDs), or diffuse parenchymal lung disorders, constitute a group of more than 150 different disorders characterised by inflammation of the lung parenchyma or interstitium, sometimes followed by the occurrence of pulmonary fibrosis. Clinical outcomes differ greatly, varying from a benign mediastinal lymphadenopathy in Lofgren's syndrome to a devastating deterioration of pulmonary function in idiopathic pulmonary fibrosis (IPF). This heterogeneous group of diseases can be divided in four major subgroups [1]: 1) ILD with a known cause or association (*e.g.* medication, metals or connective tissue disease), 2) idiopathic interstitial pneumonias (IIPs), 3) granulomatous ILD (*e.g.* sarcoidosis or hypersensitivity pneumonitis) and 4) other forms of ultra-rare ILD (*e.g.* lymphangioleiomyomatosis or pulmonary alveolar proteinosis). The group of IIPs consists of nine different entities as summarised in table 1.

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Table 1. Revised American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias (IIPs): multidisciplinary diagnoses

Major IIPs
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organising pneumonia
- Acute interstitial pneumonia (formerly known as Hamman–Rich syndrome)

Rare IIPs
- Idiopathic lymphoid interstitial pneumonia
- Pleuroparenchymal fibroelastosis

Unclassifiable IIPs #

#: causes of unclassifiable IIPs include 1) inadequate clinical, radiological or pathological data, and 2) major discordance between clinical, radiological and pathological findings that may occur in the following situations: a) previous therapy resulting in substantial alteration of radiological or histological findings (*e.g.* biopsy of desquamative interstitial pneumonia after steroid therapy, which shows only residual nonspecific interstitial pneumonia), b) new entity, or unusual variant of recognised entity, not adequately characterised by the current American Thoracic Society/European Respiratory Society classification (*e.g.* variant of organising pneumonia with supervening fibrosis), and c) multiple high-resolution CT and/or pathological patterns that may be encountered in patients with IIP. Reproduced and modified from [1] with permission.

ILDs can present as acute entities, such as the acute interstitial pneumonia formerly known as Hamman–Rich syndrome, or as a more chronic disease with or without pulmonary fibrosis. Unfortunately, a rapid deterioration can also occur during the course of chronic ILDs, presenting as an acute exacerbation. In clinical practice, most exacerbations occur in five different ILDs: sarcoidosis, IPF, idiopathic nonspecific interstitial pneumonia (iNSIP), hypersensitivity pneumonitis and collagen vascular disease (CVD)-related ILD. In this chapter, we will focus on the current insights into the pathogenesis, definitions and treatment options for these specific acute exacerbations. There are important differences in presentation, aetiology and prognosis of acute exacerbations between these different ILDs which we will outline in more detail in the following sections.

Sarcoidosis

Sarcoidosis is a multisystemic disease characterised by the formation of nonnecrotising granulomas in different organs, mostly affecting intrathoracic lymph nodes, lungs and skin [2].

The aetiology of sarcoidosis remains unknown and no curative treatment exists. Fortunately, however, not all sarcoidosis patients require treatment. It has been reported that the need for systemic treatment varies between 20% and 70% [2–4]. Main treatment indications are risk of organ failure and substantial impact on quality of life. Drugs often used are glucocorticoids, methotrexate, azathioprine or leflunomide [5]. Targeted tumour necrosis factor (TNF)-α inhibition can be used in refractory sarcoidosis patients [5].

Acute exacerbation of pulmonary sarcoidosis

Worsening of respiratory symptoms occurs frequently in patients with pulmonary sarcoidosis [6, 7]. The estimated frequency of pulmonary worsening is between 13% and 75%, based on

the definition used [8–11]. In 2012, Panselinas and Judson [12] made an excellent effort to accurately define such acute episodes of pulmonary worsening as an acute pulmonary exacerbation of sarcoidosis (APES). APES was defined as an increase of pulmonary symptoms caused by new or worsening granulomatous inflammation, combined with a decline of forced vital capacity (FVC) or FEV1 >10% compared with baseline. The term "acute" can be somewhat misleading, however, due to the fact that the symptoms should be present for at least 1 month [12]. The latter is important because airway hyperreactivity has been demonstrated in up to 58% of sarcoidosis patients [13–15]. When pulmonary complaints and decline in pulmonary function resolve in just several days, it is unlikely that an increase in granulomatous inflammation was responsible for the initial complaints. When dealing with APES it is also challenging to differentiate worsening of symptoms based on increased pulmonary granulomatous inflammation from symptoms caused by extrapulmonary sarcoidosis (cardiac localisation or pulmonary hypertension), complications of immunosuppressive treatment (*e.g.* infections, toxicity or steroid myopathy) or other conditions related to sarcoidosis (*e.g.* embolism [16, 17], depression [18], fatigue [19] or small fibre neuropathy [20]). Symptoms of APES are not specific. However, in their cohort of sarcoidosis patients presenting with APES, McKinzie *et al.* [21] demonstrated that >90% of patients experienced cough, whereas fever or night sweats seldom occurred. In clinical practice, a chest radiograph is performed routinely in patients with increased pulmonary symptoms to rule out causes other than sarcoidosis. It is important to note, however, that chest radiographs in APES are often unchained so they cannot be used to exclude APES [22]. In these patients, a CT scan should be performed in order to evaluate the lung parenchyma.

Treatment of APES

Treatment with corticosteroids is advised when a diagnosis of APES is made. In a study of 36 patients with APES treated with prednisolone the median time for normalisation of pulmonary function was only 21 days with a marked improvement of pulmonary symptoms [21]. If after 4–6 weeks no improvement on steroids is seen, an alternative diagnosis other than APES should be considered. A proposed algorithm for the treatment of APES is shown figure 1. Interestingly, sarcoidosis patients receiving steroids are also prone to develop APES. One theory is that the granulomatous inflammation in sarcoidosis is necessary for the host to clear the causative agent. If such an antigen can be cleared, the inflammatory response will terminate [23]. This granulomatous inflammation is inhibited when patients receive corticosteroids, possibly resulting in persistence of the antigen. If corticosteroids are tapered then the granulomatous inflammation will flare when the causative antigen is still present. Other risk factors for APES are listed in table 2.

Summary

Acute exacerbations of pulmonary sarcoidosis occur regularly and respond well to corticosteroids. In clinical practice it is important to rule out other causes for worsening of symptoms or pulmonary dysfunction before an accurate diagnosis of APES can be made.

Idiopathic pulmonary fibrosis

Definition of acute exacerbation in IPF

IPF is a devastating, progressive lung disease characterised by the formation of parenchymal fibrosis. It is the most common disease entity within the group of IIPs [40] and median

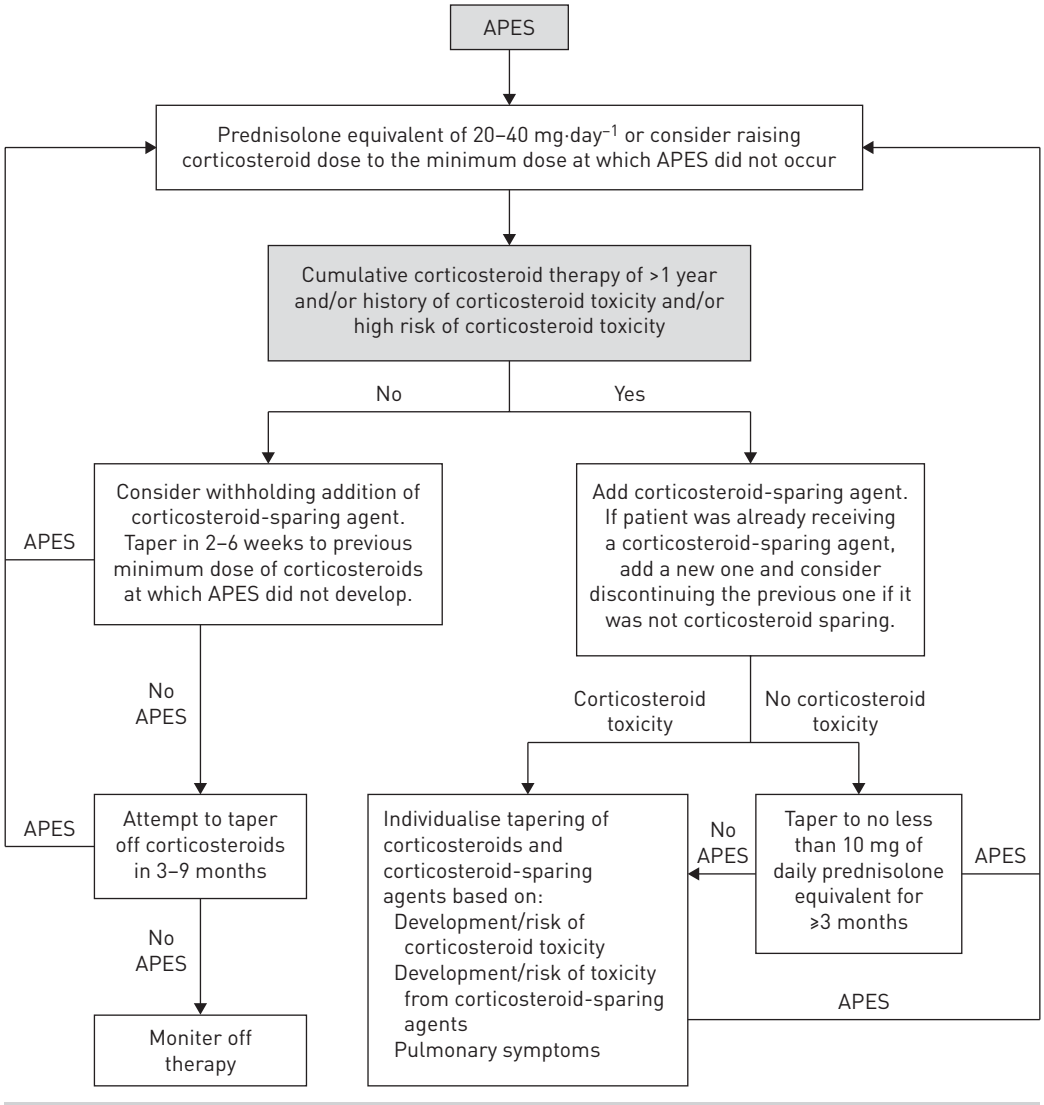
APES
Prednisolone equivalent of 20–40 mg·day^{-1} or consider raising corticosteroid dose to the minimum dose at which APES did not occur
Cumulative corticosteroid therapy of >1 year and/or history of corticosteroid toxicity and/or high risk of corticosteroid toxicity
No
Yes
Consider withholding addition of corticosteroid-sparing agent. Taper in 2–6 weeks to previous minimum dose of corticosteroids at which APES did not develop.
APES
Add corticosteroid-sparing agent. If patient was already receiving a corticosteroid-sparing agent, add a new one and consider discontinuing the previous one if it was not corticosteroid sparing.
No APES
Corticosteroid toxicity
No corticosteroid toxicity
Attempt to taper off corticosteroids in 3–9 months
APES
Individualise tapering of corticosteroids and corticosteroid-sparing agents based on:
Development/risk of corticosteroid toxicity
Development/risk of toxicity from corticosteroid-sparing agents
Pulmonary symptoms
No APES
Taper to no less than 10 mg of daily prednisolone equivalent for ≥3 months
APES
No APES
APES
Moniter off therapy

Figure 1. Proposed treatment algorithm for acute pulmonary exacerbation of sarcoidosis (APES). Reproduced and modified from [12] with permission.

survival is ~3–4 years in patients without antifibrotic treatment [41–43]. Most patients with IPF die from respiratory failure due to progression of the disease, concomitant infections or pulmonary hypertension. Respiratory failure in patients with IPF can also be precipitated by acute deterioration of the disease without an attributable cause, which has been called acute exacerbation of IPF (AE-IPF). Many different definitions of AE-IPF have been published throughout the years, eventually resulting in the first consensus definition in 2007 [44]. At that time, the following criteria had to be met for the diagnosis of AE-IPF: 1) previous diagnosis of IPF, 2) unexplained or worsening of dyspnoea within the past 30 days, 3) new bilateral areas of ground-glass attenuation or consolidations on high-resolution CT (figure 2) and 4) exclusion of other causes, such as infection, cardiac decompensation or pulmonary embolism. It was important to define consensus criteria for AE-IPF in order to obtain insights into the pathophysiology and prevalence of such exacerbations in IPF

Table 2. Risk factors for acute pulmonary exacerbation of sarcoidosis

African-American *versus* Caucasian [8, 24]
Longer disease duration (median 33 months *versus* median 10 months) [25]
Female *versus* male [8]
Older age [9]
Musculoskeletal sarcoidosis at presentation [8]
Extrapulmonary sarcoidosis [10]
Fibrocystic pulmonary sarcoidosis [9, 11]
Presence of worsening of pulmonary symptoms [8, 25, 26]
Treatment with corticosteroids or other immunosuppressive therapy (*e.g.* etanercept) [8, 10, 25–32]
Antiretroviral therapy [33–35]
Post lung transplant [36–39]

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patients. Recently, an international working group report on AE-IPF was published with a revision of the 2007 criteria for AE-IPF (table 3) [45]. An important difference is that an acute exacerbation is no longer seen as an idiopathic event but, in concordance with exacerbations in asthma or COPD, for example, can have multiple different triggers, such as infection, aspiration, drug toxicity and surgery/mechanical ventilation [45]. Furthermore, the previous 30-day time period was found arbitrary and has been changed to a more flexible time window. The authors state that the proposed revised criteria are more inclusive and practical for clinicians and researchers involved in clinical trials relating to IPF.

Based on placebo group analysis of multiple RCTs addressing new therapies in IPF, the annual incidence of AE-IPF is estimated to be between 1% and 20% [46–50]. AE-IPF has a 3-month survival rate of ∼50% and is estimated to account for up to 40% of all deaths in patients with IPF [43]. Risk factors for developing AE-IPF are low FVC, use of immunosuppressive therapy, increased BMI, absence of a smoking history [51, 52], mechanical ventilation, thoracic surgery and aspiration [53, 54].

Aetiology of AE-IPF

The aetiology of AE-IPF is unknown. It is thought that AE-IPF consists of a sudden acceleration of the underlying fibrosis in IPF [55]. The histopathology of AE-IPF most often reveals a pattern of diffuse alveolar damage (DAD) superimposed on the underlying usual interstitial pneumonia (UIP) pattern [44, 56]. The histopathological pattern of DAD is not specific for AE-IPF. It has been demonstrated that pulmonary infections, connective tissue diseases, complications of lung transplantation or exposure to radiation can also cause DAD [57, 58].

Corticosteroids and immunosuppressive drugs in AE-IPF

Treatment with corticosteroids can be beneficial in some stages of ARDS [59–61]. It is therefore not surprising that high-dose corticosteroids are often prescribed in the management of AE-IPF. Treatment of AE-IPF with high-dose corticosteroids is recommended in the international consensus statement on the diagnosis and management of IPF [62]. However, it is important to note that it is described as a weak recommendation with very low quality of evidence. In Europe, differences can be found between national

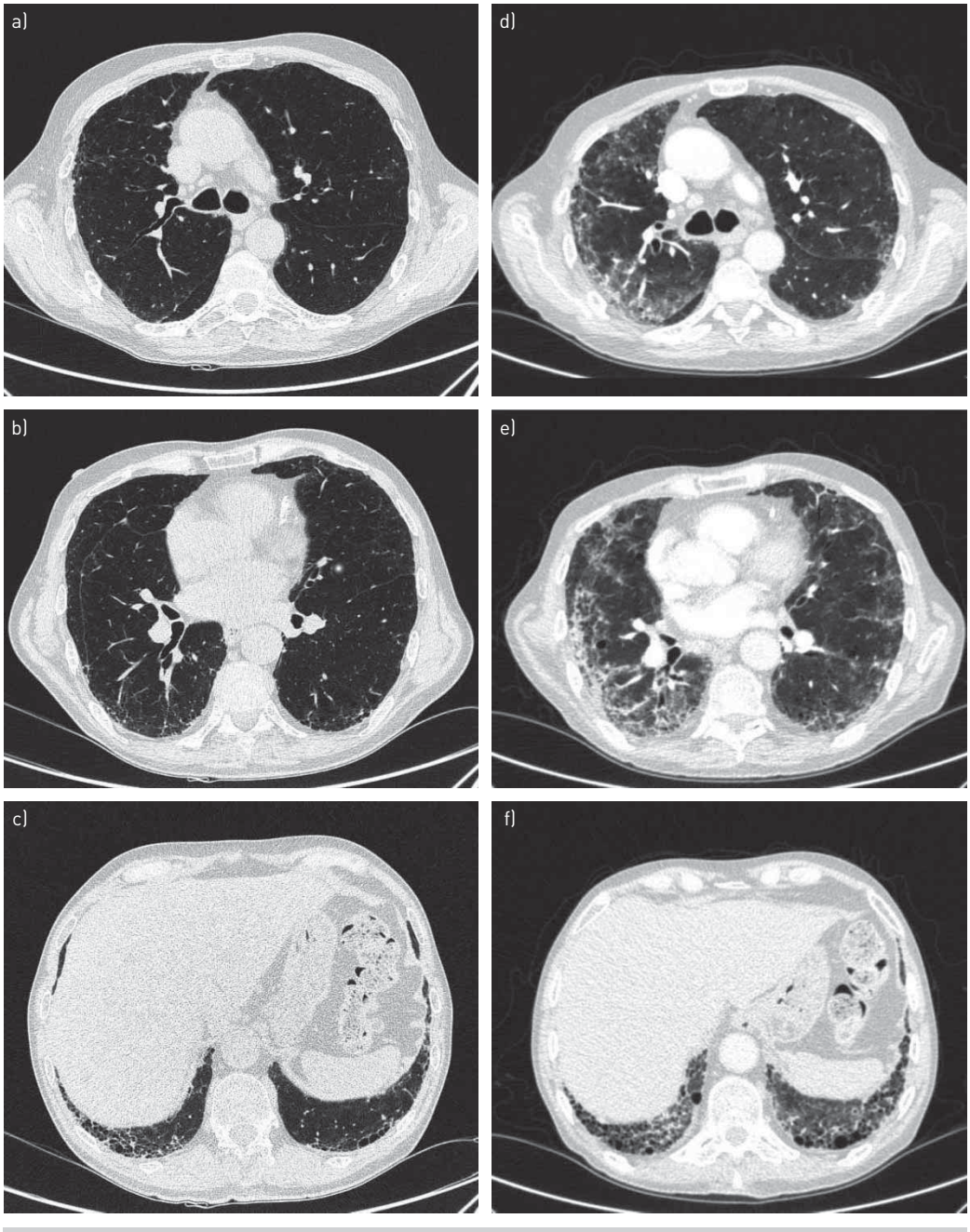

Figure 2. High-resolution CT in acute exacerbation of idiopathic pulmonary fibrosis (IPF). Patient with IPF a–c) 2 years before an acute exacerbation and d–f) at the time of an acute exacerbation. During this exacerbation, bilateral ground-glass opacities can be seen superimposed on the already existing usual interstitial pneumonia pattern. The patient survived, but became oxygen dependent.

guidelines for the treatment of AE-IPF. The French practical guideline for the treatment of AE-IPF, for example, recommends the use of high-dose steroids, but also mentions that intravenous cyclophosphamide can be given [63]. The Dutch guideline for the treatment of IPF recommends not using high-dose steroids during AE-IPF in the majority of patients [64].

Table 3. Proposed revised definition and criteria for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF)

Revised definition
An acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality
Revised diagnostic criteria
Previous or concurrent diagnosis of IPF[#]
Acute worsening or development of dyspnoea, typically <1 month duration
CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia[¶]
Deterioration not fully explained by cardiac failure or fluid overload

Events that are clinically considered to meet the definition of AE-IPF but fail to meet all four diagnostic criteria owing to missing CT data should be termed "suspected acute exacerbations". [#]: if the diagnosis of IPF is not previously established, this criterion can be met by the presence of radiological and/or histopathological changes consistent with the usual interstitial pneumonia pattern on the current evaluation; [¶]: if no previous CT is available, the qualifier "new" in the definition can be dropped. Reproduced and modified from [45] with permission.

Both guidelines are based on expert opinions and no RCTs regarding the use of corticosteroids in AE-IPF exist.

A rationale for using steroids is the possibility of a superimposed histological pattern of organising pneumonia during AE-IPF. Unfortunately, retrospective studies of different patient cohorts with AE-IPF treated with high-dose steroids persist in demonstrating high mortality rates [52, 53, 65]. Furthermore, elevated C-reactive protein levels, leukocytosis, and increased levels of interleukin-8, α-defensin and ST2 protein in AE-IPF suggest a triggered immune response [44, 65, 66]. Multiple studies, often retrospectively in a small cohort, evaluated the combination of steroids and immunosuppressive therapy, such as tacrolimus, cyclosporine, azathioprine or cyclophosphamide [67–72], with positive outcomes. However, RCTs are still needed to prove the efficacy of immunosuppressive treatment in AE-IPF. With regard to the use of azathioprine, it is has become clear that use in patients in a stable phase of their IPF does not prevent the occurrence of AE-IPF and, more strikingly, may even increase its incidence [73].

Interestingly, in the field of ARDS research, two new clinical ARDS phenotypes have been described recently [74]: phenotype I demonstrates low inflammatory markers and shock, phenotype II demonstrates high plasma levels of inflammatory markers, severe shock and metabolic acidosis. This could be in line with the observation made by Lorente *et al.* [75] that a histological pattern of DAD was found in only 33% of patients with ARDS on autopsy, and may be the first step in predicting which patients with ARDS would benefit from immunosuppressive therapy. Hopefully, similar research in AE-IPF will be performed that helps determine criteria for the identification of a subgroup that benefits from corticosteroids.

Antibiotics in AE-IPF

Due to the fact that most patients presenting with AE-IPF are not eligible for invasive diagnostic procedures such as bronchoscopy, the majority will receive empiric treatment with antibiotics [76]. The use of haemoperfusion with polymyxin B, a cationic polypeptide antibiotic, has been studied in patients with AE-IPF [77]. Haemoperfusion with a polymyxin B-immobilised fibre column can absorb endotoxins, such as lipopolysaccharide,

reactive oxygen species and neutrophils, and benefits patients with septic shock [78]. Its use has also been studied in patients with ARDS with improvement of oxygenation [79]. In a retrospective small cohort study, Enomoto *et al.* [77] reported an improved survival of patients with AE-IPF treated with polymyxin B haemoperfusion. Further prospective RCTs are needed to definitely determine its value in the treatment of patients with AE-IPF.

Antifibrotic drugs in AE-IPF

Since the adjusted guideline on diagnosis and treatment of IPF [80], the antifibrotic drugs pirfenidone and nintedanib have become the standard of care in patients with mild to moderate IPF. In the first prospective trial using pirfenidone in IPF patients, a lower incidence of AE-IPF was observed in the treatment group [81]. In the following three worldwide RCTs (CAPACITY-1, CAPACITY-2 and ASCEND), the incidence of AE-IPF was not a specified end-point [82, 83]. When patients using pirfenidone develop AE-IPF the clinician has to decide whether to stop or continue the drug. In a *post hoc* analysis of the above-mentioned trials it has been shown that patients with a clinically meaningful decline in pulmonary function during treatment with pirfenidone can benefit from continuation of therapy. In particular, continued use of pirfenidone reduced the risk of a second decline of >10% FVC or death compared with placebo [84]. These analyses suggest a benefit for patients when continuing pirfenidone; however, this has not been studied specifically in any trial. A decrease in the frequency of AE-IPF was seen in the phase 2 trial addressing dose finding and safety of nintedanib in patients with IPF [46]. In the following RCTs (INPULSIS-1 and INPULSIS-2) a reduction of AE-IPF was only demonstrated in the latter trial [85]. It was found that nintedanib had a significant benefit compared with placebo in a pre-specified sensitivity analysis on the pooled data on the time to the first adjudicated acute exacerbation [85].

However, in concordance with pirfenidone, studies specifically addressing continuation of nintedanib in patients with AE-IPF are also lacking. A *post hoc* analysis of the INPULSIS trials could suggest a benefit of continuation of nintedanib in patients after AE-IPF. This is based on the observation that the effect of nintedanib seemed to be present only in the most severe patients (FVC <70%) [86].

N-acetylcysteine (NAC) is a precursor of the antioxidant glutathione. Based on its antioxidative effect, low costs and the promising results of the IFIGENIA trial in 2005 [87], it has been used widely in the treatment of IPF. In 2014, it was demonstrated that treatment with NAC did not favour disease outcome in patients with stable IPF [50]. Pragmatically, in some clinics NAC is still used in patients presenting with AE-IPF. Most patients with IPF are currently being treated with either pirfenidone or nintedanib. As mentioned above, there is no indication to stop these drugs in IPF patients presenting with an acute exacerbation. Interestingly, in a recent phase 2 study comparing pirfenidone with pirfenidone and NAC combination treatment, data suggested that addition of NAC to pirfenidone could even be harmful in patients with IPF [88]. This indicates that currently there is no rationale left for the use of NAC in IPF patients with either stable disease or acute exacerbations.

Anticoagulants in AE-IPF

An important aspect in the pathogenesis of IPF is alveolar epithelial cell injury resulting in an abnormal wound-healing response leading to fibrotic remodelling. The coagulation cascade is thought to be involved in normal wound healing [89]. In a small prospective cohort study where patients were assigned to receive prednisolone alone or prednisolone plus

anticoagulant therapy it was suggested that adding anticoagulant therapy had a beneficial effect on survival in patients with IPF [90]. Unfortunately, in the following ACE-IPF (Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis) trial, a double-blind RCT of warfarin in IPF patients, it was demonstrated that the use of anticoagulants in patients with stable disease or AE-IPF was potentially harmful [91]. In line with this result, KREUTER *et al.* [92] recently described the negative effect of medically initiated anticoagulation on mortality and other clinical outcomes in patients with IPF.

Mechanical ventilation during AE-IPF

As mentioned above, AE-IPF has a 3-month survival rate of ∼50% and is estimated to account for up to 40% of all deaths in patients with IPF [43]. Multiple small case series reported very high in-hospital mortality rates of IPF patients treated with mechanical ventilation, even up to 90% [93–96]. In the 2011 guidelines for the diagnosis and management of IPF [62], a recommendation was made to consider mechanical ventilation in only a small minority of IPF patients. Once again, published data on a large cohort of IPF patients undergoing mechanical ventilation was not available at that time. Recently, in a nationwide retrospective cohort analysis, RUSH *et al.* [97] described 17 770 hospitalisations of IPF patients, of whom 1703 patients received mechanical ventilation and 778 received noninvasive mechanical ventilation. The mortality of IPF patients receiving mechanical ventilation in this cohort was ∼50%, a much better outcome than thought previously. Obviously, not all patients in this cohort were ventilated during AE-IPF and there was no stratification for disease severity. It could be that the most severe IPF patients did not receive mechanical ventilation, based on previous indications of very high mortality rates. At most, these data suggest that the outcome in IPF patients receiving mechanical ventilation could be better than expected previously.

Therefore, the decision about whether to intubate a patient with AE-IPF should be discussed case by case, preferably in a multidisciplinary setting, taking into account issues such as the presence of a potentially reversible cause of the exacerbation, opportunity for lung transplantation, availability and/or response to antifibrotic drugs, and expectations and values of the patient and their family.

Summary

In IPF patients presenting with symptoms suggesting AE-IPF, acute worsening from extraparenchymal causes (*e.g.* pulmonary embolism or congestive heart failure) should first be ruled out. If there is AE-IPF then the clinician should try to identify triggers, such as infection, medication capable of inducing ILD or aspiration, and treat accordingly (figure 3). International evidence-based guidelines addressing the management of IPF make a weak recommendation for the use of corticosteroids during AE-IPF based on anecdotal reports and the high mortality rate. The use of mechanical ventilation should be discussed case by case, addressing issues such as lung transplantation, change of reversibility and expectations of patients.

Pulmonary fibrosis other than IPF

Frequency of acute exacerbations in non-IPF fibrotic pulmonary disease

Acute exacerbations are not seen solely in patients with IPF. Acute exacerbations have been also described in patients with fibrotic interstitial pneumonias, such as iNSIP, interstitial

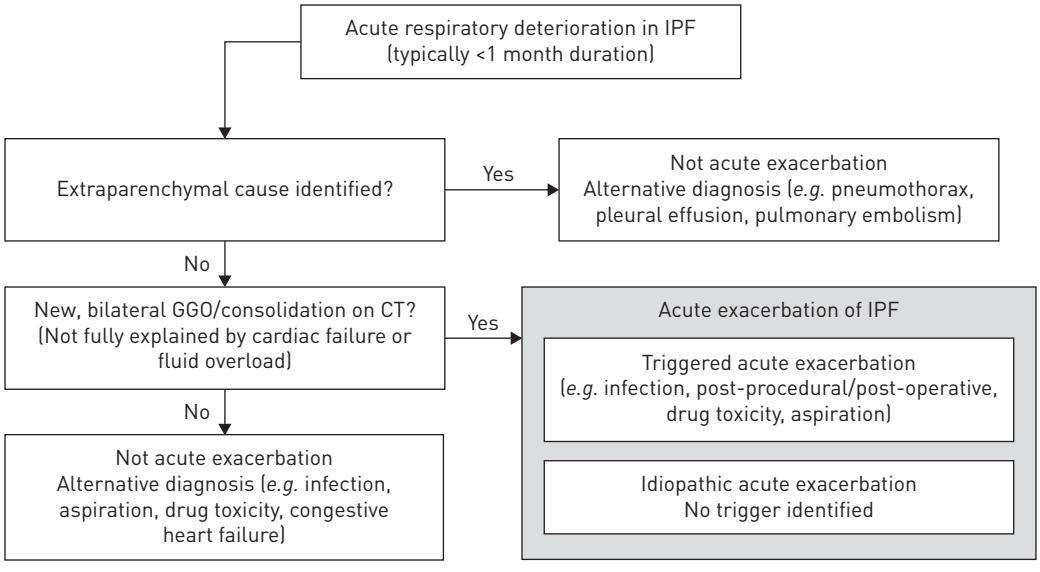
Acute respiratory deterioration in IPF
(typically <1 month duration)
Extraparenchymal cause identified?
Yes
Not acute exacerbation
Alternative diagnosis (e.g. pneumothorax, pleural effusion, pulmonary embolism)
No
New, bilateral GGO/consolidation on CT?
(Not fully explained by cardiac failure or fluid overload)
Yes
Acute exacerbation of IPF
Triggered acute exacerbation
(e.g. infection, post-procedural/post-operative, drug toxicity, aspiration)
Idiopathic acute exacerbation
No trigger identified
No
Not acute exacerbation
Alternative diagnosis (e.g. infection, aspiration, drug toxicity, congestive heart failure)

Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorised as extraparenchymal (*e.g.* pulmonary embolism, pneumothorax or pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification (GGO)/consolidation on CT that is not fully explained by cardiac failure or fluid overload are categorised as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (*e.g.* infection). Acute exacerbations are further categorised as triggered acute exacerbations or idiopathic acute exacerbations, depending on whether an underlying trigger for acute exacerbation is found. Reproduced and modified from [45] with permission.

pneumonia associated with CVD and chronic hypersensitivity pneumonitis [52, 95–105]. In a retrospective cohort study, Park *et al.* [106] described the estimated 1-year frequency of an acute exacerbation in iNSIP of 4.2%. It is important to note that all patients in this study underwent a surgical lung biopsy to confirm the diagnosis and in two of the 74 iNSIP patients an acute exacerbation developed immediately after surgery. The clinical features of patients with exacerbations of iNSIP were similar to those of AE-IPF, except that patients with an acute exacerbation of iNSIP were younger and predominantly female [106]. As mentioned above, acute exacerbations can also occur in CVDs, such as systemic sclerosis, Sjögren's disease, rheumatoid arthritis, polymyositis/dermatomyositis, mixed connective tissue disease and systemic lupus erythematosus. Suda *et al.* [98] described a cohort of 83 patients with ILD based on CVD. The overall incidence of acute exacerbation was 7.2% with an annual incidence of 1.3%. Acute exacerbation was most commonly found in patients with rheumatoid arthritis, perhaps based on the fact that in rheumatoid arthritis, in comparison with other CVDs, a UIP pattern is the most common underlying ILD. This observation was also found in a study of Tachikwa *et al.* [107] where 40% of CVD patients with an acute exacerbation had rheumatoid arthritis, 40% had dermatomyositis and 20% has systemic sclerosis. The overall 3-month mortality in this study of patients with underlying CVD presenting with an acute exacerbation was significantly lower compared with patients with AE-IPF (33% *versus* 69%). According to underlying CVD, 3-month mortality was 17% in rheumatoid arthritis, 50% in dermatomyositis and 33% in patients with systemic sclerosis [107]. Tapering of corticosteroids within 1 month preceded the development of an acute exacerbation in 27% of patients with CVD. In chronic hypersensitivity pneumonitis, Miyazaki *et al.* [108] described

an overall incidence of acute exacerbation of 14%. Not surprisingly, the frequency of an acute exacerbation was significantly higher in hypersensitivity pneumonitis patients with a UIP pattern compared with hypersensitivity pneumonitis patients with a fibrotic NSIP pattern [108]. The mortality is very high (86–100%).

Treatment

Obviously, the rationale for using steroids or immunosuppressive drugs in acute exacerbations of non-IPF pulmonary fibrosis such as CVD-related interstitial pneumonia is much stronger compared with that for treating AE-IPF. This is based on the underlying immunological mechanisms of this disease group. As in AE-IPF, in patients presenting with symptoms suggesting an acute exacerbation, acute worsening from extraparenchymal causes such as pulmonary embolism or congestive heart failure should first be ruled out. If there is an acute exacerbation then the clinician should try to identify triggers, such as infection, medication capable of inducing ILD and aspiration, and treat accordingly. Most patients with pulmonary fibrosis based on CVD, iNSIP or hypersensitivity pneumonitis are treated with steroids with or without immunosuppressive drugs. Therefore, the treating clinician should be extra aware of underlying opportunistic infections, such as *Pneumocystis jiroveci* [109, 110]. Furthermore, immunosuppressive drugs themselves, such as methotrexate, TNF-α inhibitors, tocilizumab and rituximab, can cause ILD [111]. High-dose corticosteroids, cyclophosphamide or rituximab can be used when treating acute exacerbations in non-IPF pulmonary fibrosis [112, 113].

Summary

Acute exacerbations can occur in patients with non-IPF pulmonary fibrosis, such as iNSIP, CVD-related ILD or fibrotic hypersensitivity pneumonitis. During the management, a similar approach as for the evaluation of acute respiratory worsening in AE-IPF can be followed. However, based on the fact that many patients will have used immunosuppressive drugs, an extra focus should be on excluding opportunistic infections and drug toxicity. Using high-dose corticosteroids, cyclophosphamide or rituximab is advised when treating these acute exacerbations.

Conclusions

Acute exacerbations occur over a broad spectrum of ILDs, such as sarcoidosis, IPF, iNSIP, hypersensitivity pneumonitis and CVD-related ILDs. There are important differences in the presentation, aetiology and prognosis of acute exacerbations between these different ILDs. In sarcoidosis, acute exacerbations in general respond very well to corticosteroids and have a good prognosis based on reversibility. On the contrary, in more fibrotic diseases such as IPF, an effective response to corticosteroids during an acute exacerbation is less likely, making such events often fatal. It is becoming increasingly recognised that an acute exacerbation in fibrotic ILD does not necessarily have to be idiopathic, but can be provoked by various triggers, such as infection, mechanical ventilation, drug toxicity and aspiration. Decisions regarding mechanical ventilation in patients with acute exacerbations of ILD are challenging and should be discussed case by case, preferably in a multidisciplinary setting. Future trials studying new treatment options for patients with acute exacerbation in ILDs are eagerly awaited.

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Chapter 9

Severe haemoptysis

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Haemoptysis may be life threatening, with a mortality rate >50% in the absence of early and adequate management. Evaluation of the severity of haemoptysis is crucial to determine the most appropriate treatment in a timely fashion. The therapeutic management of severe haemoptysis has improved considerably with the advances in vascular interventional radiology, with thoracic surgery being reserved for failure of endovascular treatment or focal lesions at high risk of bleeding recurrence in selected patients. Evaluation of therapeutic strategies targeted on the risk of adverse outcomes and mortality is necessary to refine the management of severe haemoptysis and improve its prognosis.

Haemoptysis is a common symptom accounting for 15% of recruitment in pneumology or thoracic surgery wards [1–3]. In a few cases (5–10%), haemoptysis may be life threatening, with a mortality rate >50% in the absence of early and adequate management [4–7]. A methodical reasoning and a rigorous algorithm of management may improve the prognosis of severe haemoptysis [1, 8, 9].

Here, we will focus on haemoptysis related to systemic bronchial and nonbronchial arteries or pulmonary artery involvement. More rarely, haemoptysis may be related to injury of the alveolar/capillary barrier. Alveolar haemorrhage should be suspected in case of haemoptysis, anaemia and diffuse bilateral infiltrates with a peri-bronchovascular disposition. Alveolar haemorrhage is mainly related to immune disorders and cardiac dysfunction, although infectious diseases may account for a few cases [10].

Definition, pathogenesis, mechanism(s) and aetiologies

Severe haemoptysis is a life-threatening expectoration of blood originating from the lower respiratory tract, by virtue of airway obstruction and/or alveolar inundation or blood loss [11].

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The lungs are supplied by a dual vasculature involving the systemic bronchial arteries (nutritional role) and the pulmonary arteries (functional role) [12]. Physiological connections exist between both systems, at different anatomical levels (bronchopulmonary, pre-capillary, capillary and post-capillary) (figure 1).

In most cases (90%), blood may enter into the bronchi from the systemic arteries (bronchial and nonbronchial) [1, 13–16]. The pulmonary system, mainly arterial, is implicated in 5–10% of cases [1, 9, 17–19], while post-capillary anastomosis is involved in a minority of cases (*e.g.* pulmonary vein stenosis, fibrosing mediastinitis and mitral stenosis) [20, 21]. Exceptionally, large intrathoracic vessels may be involved (*e.g.* aortobronchial fistula, bronchopulmonary sequestration or tumoural invasion of a large vessel) [22–25].

The bronchial arteries arise from the descending thoracic aorta, at the level of the T5/T6 vertebrae, and may originate directly from the aorta or from a right broncho-intercostal trunk. Several anatomic variants have been described. The anterior spinal artery usually arises from a left intercostal artery, but may arise from a right intercostal artery originating from the right broncho-intercostal trunk in 3% of cases. For direct collaterals of bronchial arteries, the inferior oesophageal artery (arising directly from the aorta or from the left inferior bronchial artery) may be injured during bronchial artery embolisation [25–30].

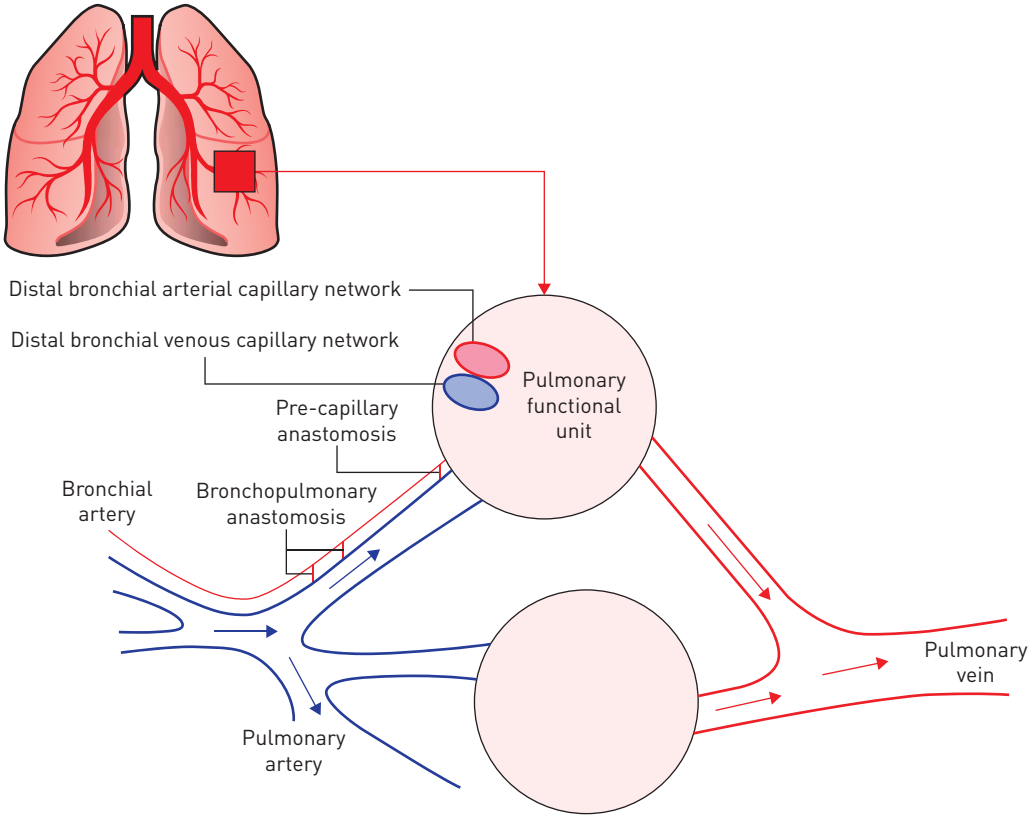

Figure 1. The dual vasculature of the lungs. The bronchial veins are not represented in the figure.

Regional vascular remodelling and neoangiogenesis may develop within the systemic bronchial and nonbronchial vessels, conversely to the pulmonary vessels [31, 32], under the following pathological conditions: 1) reduction in the proximal pulmonary blood flow (*e.g.* congenital pulmonary stenosis, pulmonary embolism and pulmonary vasculitis such as Takayasu arteritis or Behçet disease [33–36]), 2) destruction of the cartilage support of the bronchial wall induced by a chronic inflammatory process (*e.g.* bronchiectasis and cystic fibrosis) [37–39] and 3) lung cancer [1, 12, 40, 41].

A wide range of aetiologies of severe haemoptysis have been reported, among which chronic inflammatory conditions and infectious diseases, including bronchiectasis, cystic fibrosis, tuberculosis, mycetoma and lung cancer, are the most common and account for 80% of all cases [37, 38, 42, 43] (table 1). Despite a thorough aetiological investigation, 15% of severe haemoptysis cases remain with no identified cause. Cryptogenic haemoptysis may be massive; active smoking and airway inflammation could be contributing factors [44–46]. In abundant cryptogenic haemoptysis, ectopic bronchial arteries have been identified in very superficial positions, contiguous to the bronchial mucosa, with disruption of the arterial wall in the bronchial lumen (bronchial Dieulafoy syndrome). The exact prevalence of these vascular abnormalities is not known [45, 46].

Table 1. Main aetiologies of severe haemoptysis

Tumour
Lung cancer
Carcinoid tumour
Infectious diseases
Tuberculosis: active and sequelae
Aspergillus disease: mycetoma; invasive pulmonary aspergillosis
Necrotising pneumonia; lung abscess
Parasitic infection
Bronchopulmonary diseases
Bronchiectasis
Cystic fibrosis
Acute and chronic bronchitis
Miscellaneous
Sarcoidosis
Endometriosis
Coagulation disorders
Vascular pulmonary diseases
Acute pulmonary embolism and chronic thromboembolic pulmonary hypertension
Pulmonary aneurysm and pulmonary artery pseudo-aneurysm
Pulmonary arteriovenous malformations
Pulmonary arterial hypertension
Pulmonary malformations
Cardiovascular diseases
Congenital heart diseases
Pulmonary venous hypertension
Aortobronchial fistula
Trauma/foreign body
Aspirated foreign body
Tracheovascular fistula
Pulmonary arterial catheter induced pulmonary pseudo-aneurysm
Cryptogenic
Bronchial Dieulafoy disease

Severity assessment of haemoptysis

Evaluation of the severity of haemoptysis is crucial to target the most appropriate management in a timely fashion, but remains without consensus [11]. First, the terminologies used (*e.g.* "life-threatening", "massive" or "exsanguinating" haemoptysis) may refer to heterogeneous populations of patients and different clinical situations [11, 15, 16, 47, 48]. Second, the severity criteria vary, including those related to the patient (*i.e.* comorbid conditions or bleeding diathesis [2, 15]) and those associated with the bleeding event or its consequences (*i.e.* abundance [11, 15, 16, 47], mechanism (pulmonary arterial involvement), cause (*e.g.* lung cancer [40], mycetoma [1, 8, 49] or necrotising pneumonia [49–51]) and respiratory or haemodynamic consequences [9, 11, 16, 47]). When taken together, the most commonly reported severity criteria are the abundance of haemoptysis [9, 11, 47], the need for hospitalisation [47], the administration of systemic vasoconstrictors [15], the need for mechanical ventilation, vasoactive drugs or blood products [9, 11, 47] and, ultimately, the occurrence of death [9, 47].

Expectorated blood volume or flow

It is commonly accepted that the quantitative criterion "expectorated blood volume or flow" is associated with in-hospital mortality [2, 4, 7]. The abundance of haemoptysis is not easy to assess before admission in clinical practice and may be misestimated. However, after admission, the estimation of the abundance of haemoptysis may be helpful, using samples with a known volume (such as a glass, spoon, *etc.*). The reported thresholds of volume/flow vary greatly across the literature, ranging from 100 mL per 24 h to 1000 mL per 48 h [11, 47]. The volume of conductive airways is ∼250 mL and some authors therefore evaluate the risk of asphyxiation as volumes >400 mL [52].

Magnitude of bleeding effects

The respiratory and haemodynamic consequences of haemoptysis may also contribute to the characterisation of the severity of haemoptysis [9, 11, 16, 47]. However, the administration of mechanical ventilation for acute respiratory failure (ARF) only applies to 15–20% of the patients admitted to the ICU [9, 53]. In addition, the haemodynamic consequences of haemoptysis (shock) are unusual, and delayed, except when mechanical ventilation is required [9]. Lastly, the radiological extent of the alveolar flooding may be indicative of the amount of bleeding, use of mechanical ventilation and in-hospital mortality [54].

Comorbid conditions

Comorbidities, especially chronic lung diseases, cardiovascular diseases and bleeding diathesis, are also deemed to be severity criteria [1, 2, 9, 15, 38, 40].

Analysis of the mechanism and cause of haemoptysis

Most episodes of severe haemoptysis are related to the regional development of a bronchosystemic hypervascularisation. There has been a gradual change in the aetiologies of haemoptysis over the past decades, with chronic infectious processes or inflammatory lung diseases, including lung cancer, bronchiectasis, tuberculosis (active and sequelae) and mycetoma, being the most prevalent [1, 6, 15, 40, 55, 56]. Severe haemoptysis related to

bronchiectasis may involve almost exclusively the bronchial and nonbronchial systemic vasculature. Conversely, haemoptysis related to lung cancer or infectious and inflammatory diseases (Rasmussen aneurysm, necrotising pneumonia, aspergillosis and Hughes–Stovin syndrome) may be related to the involvement of the pulmonary arterial vasculature, the latter being either concomitant to a systemic hypervascularisation or occurring secondarily over time [18, 57–59].

The different steps of the therapeutic decision-making process

The therapeutic decision should be based on the following thorough step-by-step reasoning: 1) positive diagnosis of haemoptysis, 2) severity assessment and site of haemoptysis, 3) diagnosis of the mechanism of haemoptysis, and 4) diagnosis of the cause of haemoptysis (figure 2).

Positive diagnosis

The diagnosis of haemoptysis is easy in most cases [43, 60]. However, pseudo-haemoptysis (gastrointestinal or ear, nose and throat (ENT) bleeding) may mimic haemoptysis in 3–10% of cases [61, 62] and should always be considered.

Once the diagnosis of haemoptysis has been established, it should be determined if the bleeding arises from the bronchi or the alveoli. Alveolar haemorrhage should be suspected in the case of combined haemoptysis, anaemia and chest radiograph diffuse bilateral infiltrates. A CT scan shows a diffuse alveolar and interstitial syndrome, with a subpleural location, and

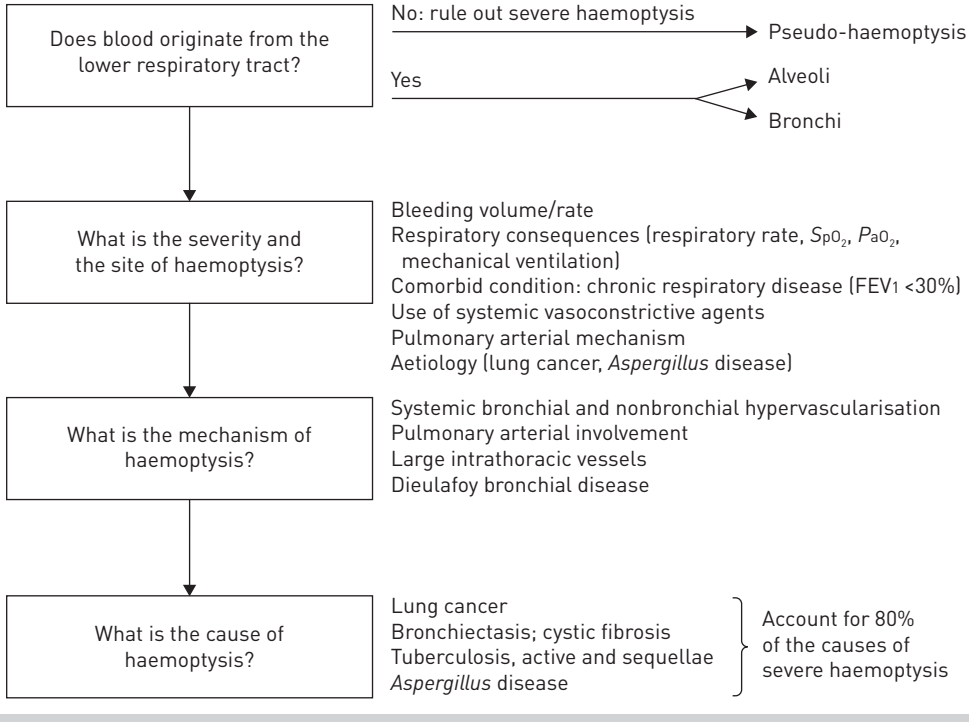
Does blood originate from the lower respiratory tract?
No: rule out severe haemoptysis
Pseudo-haemoptysis
Yes
Alveoli
Bronchi
What is the severity and the site of haemoptysis?
Bleeding volume/rate
Respiratory consequences (respiratory rate, S_{pO_2}, P_{aO_2}, mechanical ventilation)
Comorbid condition: chronic respiratory disease (FEV_1 <30%)
Use of systemic vasoconstrictive agents
Pulmonary arterial mechanism
Aetiology (lung cancer, *Aspergillus* disease)
What is the mechanism of haemoptysis?
Systemic bronchial and nonbronchial hypervascularisation
Pulmonary arterial involvement
Large intrathoracic vessels
Dieulafoy bronchial disease
What is the cause of haemoptysis?
Lung cancer
Bronchiectasis; cystic fibrosis
Tuberculosis, active and sequellae
Aspergillus disease
Account for 80% of the causes of severe haemoptysis

Figure 2. The different steps of the therapeutic decision-making process.

no signs of pulmonary oedema (no cardiomegaly, no pleural effusion). BAL revealing an increasingly bloody lavage fluid and/or a siderophagic alveolitis is the cornerstone of the diagnosis [10]. Of note, diffuse infiltrates may also result from inhalation of massive haemoptysis. Extrathoracic clues such as renal involvement may be helpful to differentiate alveolar haemorrhage from inhalation related to massive haemoptysis.

Severity assessment

The assessment of the severity of haemoptysis [11] is based on the abundance of haemoptysis [9, 11, 47], administration of a systemic vasoconstrictor [15], use of mechanical ventilation, vasoactive drugs or blood products [9, 11, 47] and, ultimately, death [9, 47]. It is noteworthy that most of these severity criteria are based on management practices, which may vary widely across centres, countries, technical facilities, *etc.* We recently attempted to identify early factors for in-hospital mortality, aiming at developing a simple prognostic rule available in the early hours of ICU admission as an aid to therapeutic decision making [9]. Among 1087 patients, 71 (6.5%) died during hospitalisation. In patients mechanically ventilated (n=80), hospital mortality reached 32.5%. Factors independently associated with in-hospital mortality were chronic alcoholism, cause of haemoptysis (especially lung cancer and aspergillosis), radiological extent of bleeding and administration of mechanical ventilation or vasoactive drugs. A pulmonary arterial mechanism was marginally significant. A score system including chronic alcoholism (1 point), cancer (2 points) or aspergillosis (2 points), pulmonary arterial mechanism (1 point), radiological extent (1 point) and mechanical ventilation (2 points) was used to classify the patients; accordingly, the probability of in-hospital mortality was 1% for score 0, 2% for score 1, 6% for score 2, 16% for score 3, 34% for score 4, 58% for score 5, 79% for score 6 and 91% for score 7 (area under the receiver operating characteristics curve 0.87). An external validation of this score is required before applying a therapeutic algorithm based on its use in patients with haemoptysis referred to the ICU [9].

Location

Haemoptysis may be located by physical exam and chest radiograph in 50–80% of cases [16, 63, 64], and by fibreoptic bronchoscopy in 90% of cases (when performed during active bleeding) [1, 65]. Multidetector CT angiography (MDCTA) provides a topographic diagnosis in 80–100% of cases [57, 66], by showing abnormalities reflecting the filling of the airways or the alveolar lumen with blood (*i.e.* ground-glass opacities), alveolar consolidation, atelectasis or unilateral aetiological lesion (*e.g.* tumour or aspergilloma). Exceptionally, MDCTA may show extravasation of the contrast medium into the bronchial lumen [26, 57]. If fibreoptic bronchoscopy remains essential for the aetiological diagnostic evaluation of all episodes of haemoptysis, it may be performed as a secondary technique. Indeed, there is no indication to perform it in an emergency for the topographic diagnosis of severe haemoptysis, except in cases of bilateral lung diseases for which MDCTA might not locate the bleeding (*e.g.* bilateral bronchiectasis). Thus, in our experience, the residual indications for performing fibreoptic bronchoscopy are therapeutic, at the initial phase of severe haemoptysis [65].

Mechanism and cause

The diagnostic approach to the mechanism of haemoptysis should be inseparable from that of its cause. These steps are crucial for deciding the most appropriate treatment to administer in a given clinical situation [1].

Therapeutic management of severe haemoptysis

The therapeutic decision is mainly guided by the amount of bleeding and its respiratory repercussions, the presumed mechanism and cause, and also the patient's operability and the potential resectability of the causal lesion. The therapeutic management of severe haemoptysis is based on medical measures, interventional vascular radiology and thoracic surgery. The goals are 1) symptomatic (aiming at avoiding suffocation by alveolar flooding or bronchial obstruction and controlling the bleeding) and 2) therapeutic. Respiratory rate and pulse oximetry should be monitored closely.

Medical measures

General treatment

The first part of the medical treatment is based on general measures, including bed rest, free airways, oxygenation and control of bleeding disorders.

The administration of supplemental oxygen is essential to prevent respiratory distress. The patient may be positioned on the bleeding side, if this is known. When mechanical ventilation is required (active bleeding or airways compromise), the use of a conventional large endotracheal tube (8–8.5 French) is recommended in order to perform bronchial suction and cleaning, and administer topical treatments [67–69]. A selective intubation should be preferred and is easier to place to the right, despite the exclusion of the right upper lobe bronchus. A double-lumen tube may be used [70]. Endoscopic control of the correct positioning is imperative [71, 72]. Ventilatory settings rely on the usual modalities for improving gas exchanges (FIO_2, PEEP, positioning). High levels of PEEP are recommended in the case of pulmonary arterial involvement, by reducing pulmonary blood flow and therefore pulmonary artery pressure [73]. Antimicrobial treatments are highly recommended in haemoptysis related to bronchiectasis, cystic fibrosis and lung abscess or necrotising pneumonia [38, 49–51], but are still debated in other cases. Cough suppression remains controversial [1, 47, 71].

Topical treatment (bronchoscopy techniques)

The second part of the medical treatment is based on topical measures, including chemical and mechanical measures that may be administered by flexible or rigid bronchoscopy [74].

In the case of persistent and abundant bleeding despite the administration of general measures, bronchoscopic techniques may be useful to control the bleeding, and to perform blood suction and clear the clots that may obstruct the airways. Rigid bronchoscopy may provide a more efficient suction, as compared with flexible fibreoptic bronchoscopy, but is usually performed under general anaesthesia and may require a skilled operative and a secure environment [56, 71, 74].

Different bronchoscopic techniques may be attempted. Cold saline solution lavage or epinephrine instillation may be successful [75–77]. Other vasoconstrictive agents (terlipressin, ornipressin) may also be used [78, 79]. Three studies have suggested the efficacy and safety of topical administration of ornipressin and terlipressin in the treatment of haemoptysis related to lung cancer (aerosolised ornipressin) [80] and in iatrogenic haemoptysis [78, 79]. A study comparing the two methods of administration of terlipressin in humans (*i.e.* intravenous and topical) showed that the plasma level of terlipressin was 251 times lower when it was

administered locally, as compared with a general administration, with a local effect on bronchial mucosa (pallor) and no significant circulatory side-effects [78]. Other topical haemostatic tamponades have been reported using either rigid or flexible bronchoscopy [77, 81, 82].

Mechanical tamponade using bronchial blockers or Fogarty catheters at the segment or subsegment bronchial level may be helpful temporary control measures [67–69, 83]. Lastly, bronchial cleaning may improve gas exchange [84]. Note, however, that bronchial cleaning should not remove the clots obstructing the alleged bronchial bleed territory. Bronchial biopsies should not be performed during active haemoptysis.

Systemic vasoconstrictors

The administration of a systemic vasoconstrictor (vasopressin, terlipressin) may be indicated if the measures mentioned above are unavailable or insufficient, or in the case of uncontrolled and massive bleeding [1, 15, 56, 71, 85, 86]. Terlipressin was first used in the treatment of gastrointestinal bleeding [87, 88]. It has also demonstrated its usefulness in gynaecological [89] and ENT [90] bleeding. The role of intravenous terlipressin in the treatment of severe haemoptysis has been suggested by some experimental and clinical observations [91, 92], and only one open clinical study [85]. These pharmacological agents should be used with caution in patients with coronary disease and systemic hypertension, and may compromise the success of bronchial arteriography owing to the vasoconstriction of the bronchial arteries.

Other systemic treatments may be used to control severe haemoptysis, such as tranexamic acid [28] and recombinant factor VII [93–97].

Interventional vascular radiology

Following the first reports of Remy *et al.* [30], bronchial artery embolisation (BAE) has progressively emerged as the first-line treatment of severe haemoptysis [66, 98]. The procedure has evolved and the use of microcatheters may allow very distal embolisation to be performed beyond the origin of the critical branches (middle anterior spinal artery, oesophageal branch) with safety and efficacy [99, 100]. A recent series of reports shows that severe haemoptysis may be controlled with BAE in 65–100% and 51–90% of cases in the short and medium term, respectively (table 2).

Endovascular treatment should always be performed after MDCTA (figure 3), which may help to: 1) identify the site of haemoptysis (ground-glass opacity or localised lung consolidation), although it is noteworthy that the direct radiological sign of haemoptysis, *i.e.* the extravasation of the contrast medium into the bronchial lumen, occurs in <10% of cases [46, 64, 107, 109] (figure 4); 2) haemoptysis: involvement of the pulmonary arterial vasculature (*e.g.* necrosis, pseudo-aneurysm, irregular pulmonary artery in the wall of a cavity or necrosis) (figure 4), and/or involvement of the systemic bronchial and nonbronchial arterial vasculature (*e.g.* hypertrophic and tortuous arteries, neovascularisation, or hypervascularisation shunting into the pulmonary artery or vein) (figure 5); 3) establish a comprehensive mapping of the bronchial and nonbronchial systemic arteries before performing arteriography [25, 29] (figure 6); 4) diagnose the cause of haemoptysis (tuberculosis, bronchiectasis and lung tumour account for 80% of cases) [25, 66] (figure 7); and 5) assess the abundance of haemoptysis (*e.g.* involvement of more than three lobes) [54]. When taken together, the use of MDCTA prior to endovascular treatment may improve the prognosis of severe haemoptysis [58, 110].

Table 2. Performance of endovascular treatment to control haemoptysis in the short and medium/long term

First author [ref.]	Study period	Patients n	Haemoptysis characteristics	Bleeding control		
				Immediate	1 month	>1 month
Remy [30]	1977	49	Various amounts (100–500 mL per 24 h)	41/49 (84%)	NA	35/49 (71%)
Cremashi [101]	1976–1990	209	Various amounts (100 to >300 mL per 24 h)	205/209 (98%)	NA	172/209 (82%)
Uflacker [102]	1983	33	Various amounts (26 patients >150 mL per 24 h)	26/26 (100%)	22/26 (85%)	22/26 (85%)
Uflacker [103]	1985	75	Various amounts (>150 mL per 24 h)	49/75 (65%)	NA	39/75 (52%)
Mal [15]	1985–1997	56	Various amounts	43/56 (77%)	32/56 (57%)	25/56 (45%)
Rabkin [104]	1987	306	Various amounts (120 patients >500 mL per 24 h)	278/306 (91%)	239/306 (78%)	242/306 (79%)
Hayakawa [105]	1992	63	Various amounts	50/63 (79%)	NA	36/63 (57%)
Swanson [106]	1981–2000	54	Various amounts; acute and chronic haemoptysis	51/54 (94%)	46/54 (85%)	43/54 (80%)
Ramakantan [107]	1996	140	Bleeding flow >300 mL per 24 h	102/140 (73%)	72/140 (51%)	94/140 (67%)
Wong [108]	1996–1998	16	Bleeding flow >250 mL	16/16 (100%)	9/10 (90%)	7/10 (70%)
Ong [16]	1997–2001	23	Bleeding flow >300 mL per 24 h or mechanical ventilation	20/23 (86%)	NA	15/23 (65%)
Chun [13]	2002–2008	50	Various amounts	43/50 (86%)	41/50 (82%)	66% (1 year) 56% (3 years)
Chan [53]	2000–2006	167	Bleeding flow >300 mL per 24 h (n=156) or mechanical ventilation (n=56)	155/167 (97%)	NA	74.5% (1 year) 55% (5 years)

NA: not available.

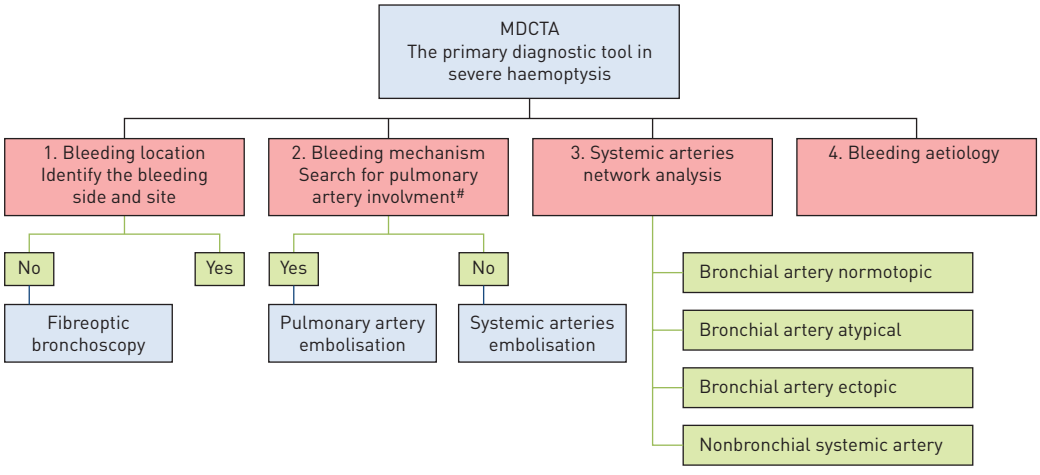

Figure 3. The role of multidetector CT angiography (MDCTA) in severe haemoptysis. #: the visualisation of contrast medium in a necrotic or excavated lesion adjoining the pulmonary artery should suggest a pulmonary arterial mechanism, especially in the case of acute or necrotic aspergillosis, acute tuberculosis (Rasmussen aneurysm), Hughes–Stovin syndrome, cancer or necrotising pneumonia. Reproduced and modified from [25] with permission.

Contraindications of BAE

In the era of MDCTA and the widespread use of microcatheters, the contraindications of BAE are very limited and the risk/benefit ratio should be assessed for each situation.

Failure of BAE

Failure of BAE may occur in 10–15% of cases, under the following situations: absence of systemic hypervascularisation, failure of vascular catheterisation, unstable catheter, vasospasm (especially when systemic vasoconstrictors have been recently administered), arterial dissection or haematoma [15, 25, 30, 49, 103, 107] and presence of a forgotten or unseen eutopic or ectopic systemic or bronchial artery involved in the haemorrhage.

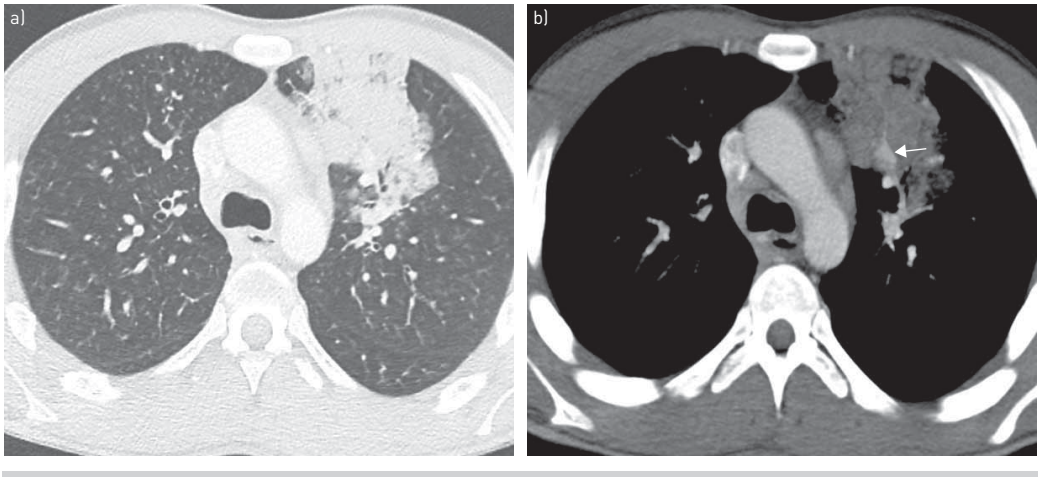

Figure 4. Pulmonary artery false aneurysm. Medical history: a 29-year-old man with a history of Behçet disease was admitted to the ICU with severe haemoptysis (300 mL per 24 h). a) Axial CT scan (lung window) shows an upper left lobe consolidation. b) Axial CT scan (maximal intensity projection, 8 mm thick; mediastinal window) shows a pulmonary artery false aneurysm (arrow) as the mechanism of haemoptysis.

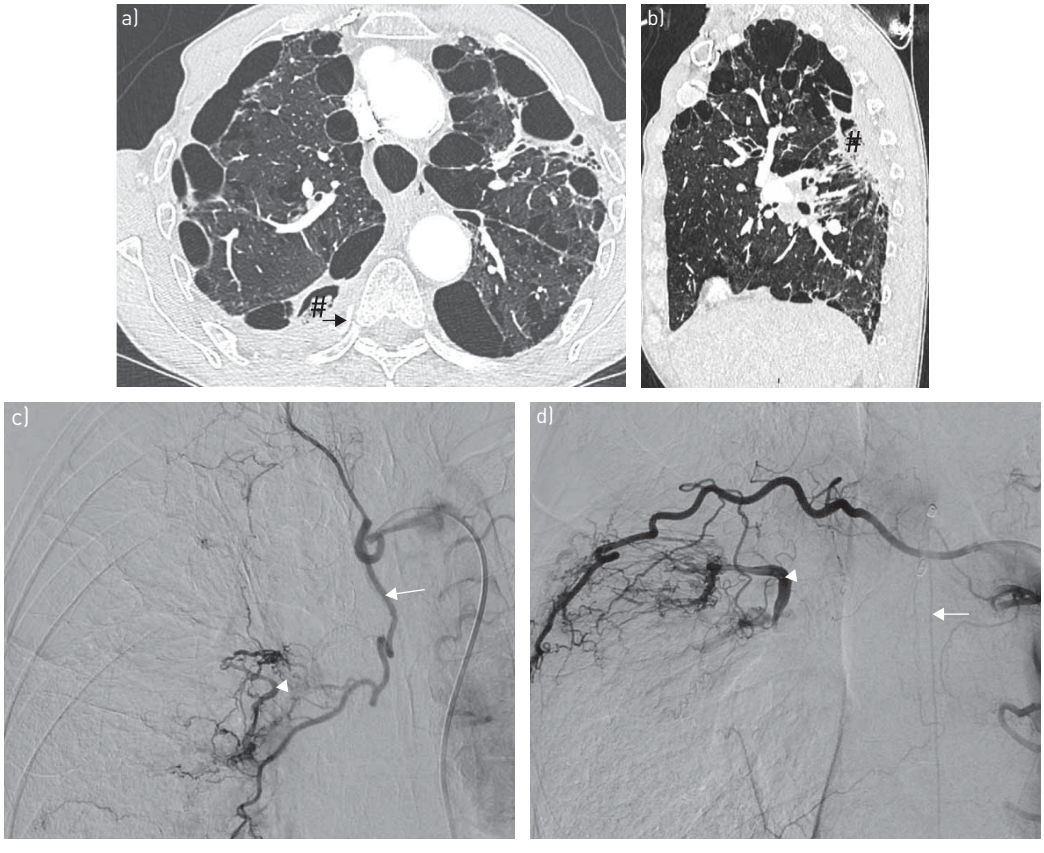

Figure 5. Systemic hypervascularisation. Medical history: a 45-year-old man with chronic aspergillosis complicating diffuse emphysema was admitted to the ICU with chronic haemoptysis (50 mL per day for 2 weeks). a) Axial and b) sagittal CT scans (parenchymal window) show a fungal ball (#) within the lung consolidation, bullous emphysema and intercostal artery enlargement (arrow). c) A right broncho-intercostal trunk angiogram shows a large bronchial artery (arrow) with systemic-to-pulmonary artery shunting (arrowhead). d) An angiogram of the eighth right intercostal artery shows an enlargement of this artery (arrow), with the same systemic-to-pulmonary artery shunting (arrowhead) as the bronchial artery in c).

Bleeding recurrences

Bleeding recurrence has been reported in 15–45% of cases [8, 47, 49].

In the short term (1 month), bleeding recurrences may be related to 1) the absence of identification of nonbronchial systemic arteries such as the internal mammary artery [13, 14, 111]; 2) a procedure performed with ongoing vasoconstrictor treatment or administered <6 h before the procedure, or with a too proximal occlusion; or 3) a pulmonary arterial mechanism, initially unknown, or an active lesion in contact with the pulmonary vasculature, such as in lung cancer, aspergillosis, cystic fibrosis, active tuberculosis and necrotising pneumonia [18, 39, 40, 102, 112, 113].

In the long term (⩾3 months), bleeding recurrences may be favoured by the persistence of the aetiology or the development of hypervascularisation [1, 53, 107, 114]. Some causes are particularly at risk of recurrence, such as aspergillosis, lung cancer and tuberculosis [13, 15, 58, 103, 115–117].

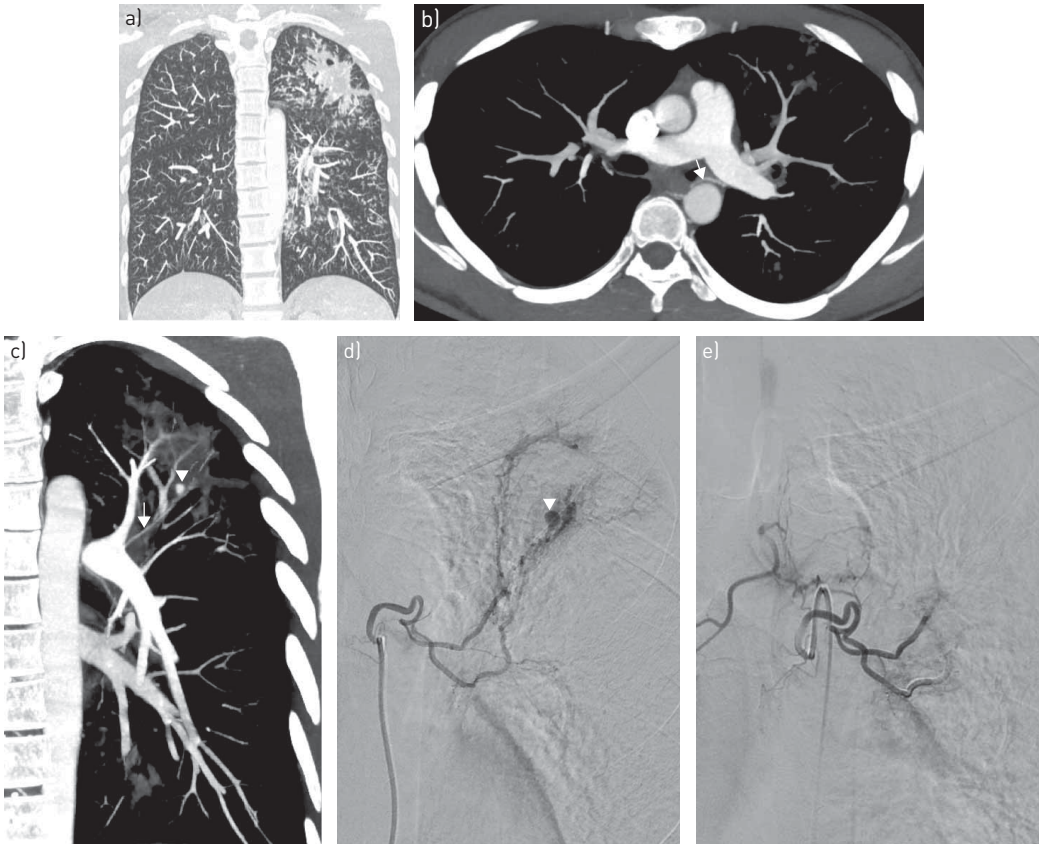

Figure 6. Bronchial artery aneurysm. Medical history: a 30-year-old man was admitted to the ICU with severe haemoptysis (300 mL per 24 h). a) A coronal maximum intensity projection CT scan (6 mm thick; parenchymal window) shows a left apical cavitation with disseminated centrolobular micronodules ("tree in bud") leading to the diagnosis of active tuberculosis and locates the bleeding in the left upper lobe. b) An axial maximum intensity projection CT scan (6 mm thick; mediastinal window) shows an enlargement of left bronchial artery (arrow). c) A coronal maximum intensity projection CT scan (15 mm thick; mediastinal window) shows a false aneurysm (arrowhead) arising from the left bronchial artery (arrow). d) A left bronchial artery angiogram confirms the presence of the false aneurysm (arrowhead) and the presence of pulmonary hypervascularisation. e) A control angiogram after embolisation of the left bronchial artery shows the complete occlusion of this artery.

Complications of BAE

Complications of BAE are rare (<5%) and dominated by vascular complications, primarily neurological [9, 43, 60–63]. Several minor complications (*e.g.* chest pain, dysphagia and subintimal dissection of the aorta) have been commonly reported [102, 111]. Serious adverse events requiring discontinuation of the procedure have been very exceptional; the frequency of these accidents is largely influenced by the operator's experience and the use of a microcatheter that allows supraselective catheterisation of the bronchial arteries [1, 15]. A recent study from our centre suggested that the systematic implementation of MDCTA before interventional radiology was associated with a reduction of the rate of failure of interventional radiology (especially in elderly patients), an increase in the indications of pulmonary angiography for pulmonary arterial occlusion and a decrease in the indications of emergency thoracic surgery [58].

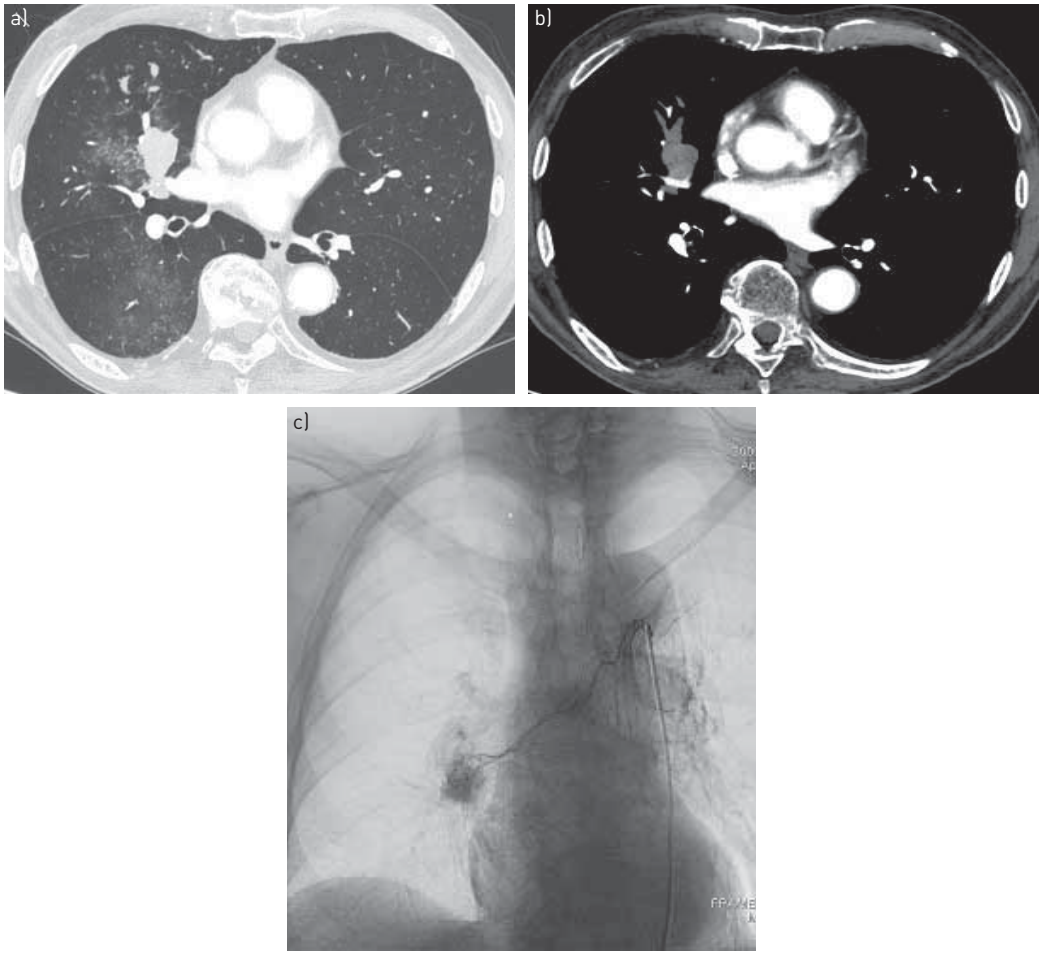

Figure 7. Bronchial artery aneurysm. Medical history: a 30-year-old man was admitted to the ICU with severe haemoptysis (300 mL per 24 h). a) Tumour obstructing the middle lobar bronchus. b) Ground-glass opacity around the tumour. c) Tumoural hypervascularisation without shunt, from a right bronchial artery from a common right/left bronchial trunk.

Pulmonary arterial involvement

In the case of pulmonary arterial involvement, pulmonary angiography with vascular occlusion using mainly coils may control the bleeding and avoid traditional surgical treatment. A transcatheter occlusion of the pulmonary arterial circulation might allow definitive and nonsurgical treatment of these vascular lesions in selected patients [1, 9, 17, 36, 40, 117]. In cancer patients, covered stents grafts have recently been successfully used to stop the bleeding [118].

Surgery

Until the late 1970s, thoracic surgery was the only treatment likely to change the immediate prognosis of severe haemoptysis, as compared with medical measures that were limited to the administration of local cold saline lavage using rigid bronchoscopy. A systematised pulmonary resection is the rule, ranging from segmentectomy to pneumonectomy, in the absence of contraindications [118]. Apical thoracoplasty may be associated, especially in the

case of tuberculous sequelae. Thoracic surgery may radically treat the cause of haemoptysis and prevent bleeding recurrence when the localised lesion has been resected [6]. The "surgical" aetiologies of severe haemoptysis have gradually changed over the past 20 years, and are dominated by bronchiectasis, tuberculosis and its complications (including mycetoma), and lung cancer [8, 86].

Thoracic surgery may be associated with a high morbidity (bronchopleural fistula, empyema, haemothorax and prolonged mechanical ventilation) and significant in-hospital mortality when performed during uncontrolled active bleeding (mortality up to 35%) and in the case of pneumonectomy [8, 84, 86]. Except for those situations during which bleeding is not controlled, the decision to perform a lung resection with the aim of preventing bleeding recurrence remains difficult and should be based on the risk/benefit ratio in each case [86]. Some situations deemed at risk of recurrence (*e.g.* cavitary lesions associated with nonbronchial systemic arteries hypervascularisation or secondary atrophic lung segments combined with a chronic infection) appear to be good surgical indications [115, 119, 120]. Conversely, bilateral lesions such as in bronchiectasis are poor candidates for surgery [86, 121–123].

The residual role of thoracic surgery has been recently investigated in the initial management of 111 patients with severe haemoptysis in the era of interventional vascular radiology [8]. 80% of the patients were operated on after a first procedure of interventional vascular radiology that controlled the bleeding in only one-third of the cases. More than half of the patients in whom the interventional vascular radiology did not control the bleeding were operated on in an emergency setting. The main indications were mycetoma, lung cancer, bronchiectasis and active tuberculosis. Altogether, surgery was performed in an emergency setting for uncontrolled active bleeding in 48 patients (43%), during the same hospital stay after bleeding control in 48 patients (43%) or planned after hospital discharge in 15 patients (14%). Three patients died during surgery and 49 (46%) developed post-operative complications. Emergency thoracic surgery, mycetoma and pneumonectomy were strongly associated with post-operative complications. 15 patients (13.5%) died in the ICU, 14 of whom had been operated on in an emergency setting. Chronic alcoholism, use of mechanical ventilation or vasoactive drugs on ICU admission and the administration of blood products prior to surgery were independent factors for ICU mortality. The majority of ICU deaths were related to haemoptysis or its complications, whereas deaths after hospital discharge (n=9) were mainly related to the causal disease [8].

Recommended strategy

The therapeutic management of severe haemoptysis should be multidisciplinary and implemented in an emergency setting. It is based on a proper assessment of the initial severity, combining the amount of bleeding and its respiratory consequences, the mechanism and cause of haemoptysis, as well as comorbid conditions.

The following algorithm may be proposed based on first-line MDCTA to guide the endovascular treatment in the case of abundant haemoptysis (>200 mL) or ARF.

In the case of successful endovascular treatment, elective thoracic surgery may be proposed to prevent recurrence, according to the patient's operability and the resectability of the causal lesion: localised lesions complicated by abundant haemoptysis or by repeated episodes of haemoptysis in the same territory (*e.g.* focal bronchiectasis and sequestration), aetiological

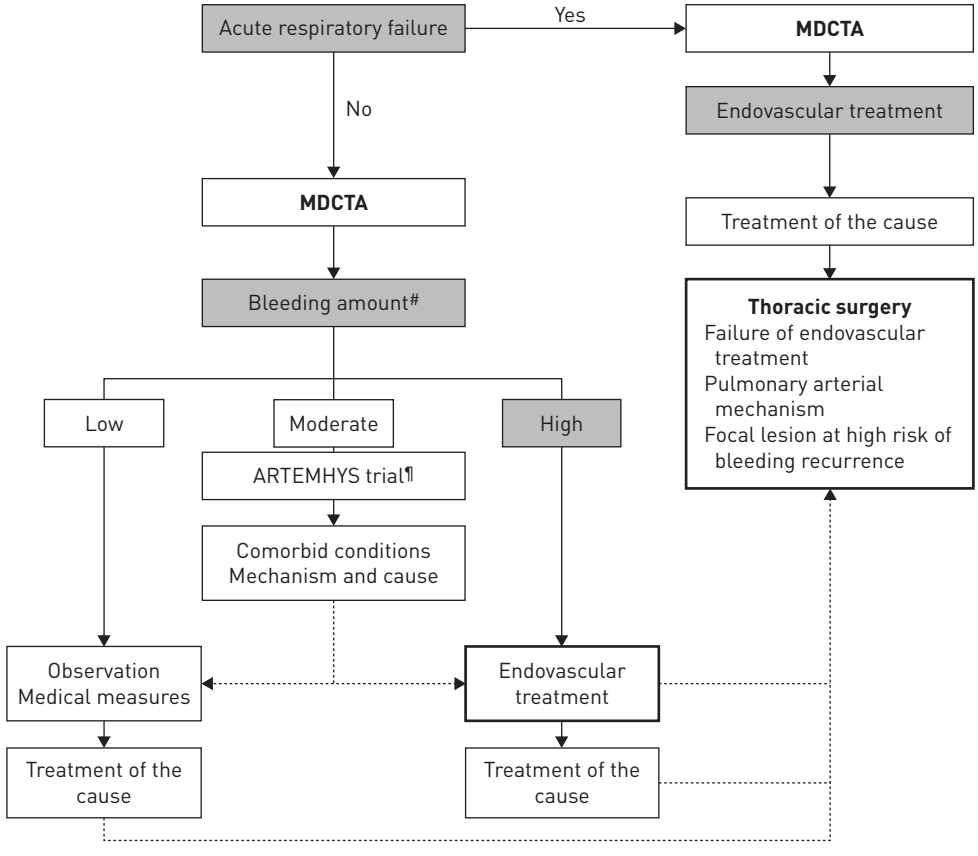

Figure 8. Recommended strategy for the management of severe haemoptysis. MDCTA: multidetector CT angiography. #: low amounts of bleeding usually refer to <100 mL; moderate amounts of bleeding usually refer to 100–200 mL; high amounts of bleeding usually refer to >200 mL. ¶: ARTEMHYS (ClinicalTrials.gov, trial number NCT01278199) is a randomised study, involving two parallel groups of patients with haemoptysis of moderate abundance (100–200 mL) related to a systemic bronchial/nonbronchial hypervascularisation, and comparing the efficacy and safety of two therapeutic strategies: bronchial artery embolisation combined with medical measures and medical measures alone. The primary outcome measure is the bleeding recurrence rate, after the initial strategy. The secondary outcome measure is the evaluation of the rate of serious adverse events, according to the therapeutic strategy during hospitalisation and the follow-up period.

lesions at risk of high amounts of bleeding or recurrence (*e.g.* focal aspergillosis and localised lung cancer), or lesions associated with proximal pulmonary arterial involvement.

If embolisation is technically impossible, and if haemoptysis persists or recurs despite one or multiple endovascular treatments, surgery should be performed in an emergency, despite its risks (figure 8).

Conclusions

Severe haemoptysis is related to chronic inflammatory and infectious diseases, of which lung cancer, bronchiectasis, tuberculosis and aspergillosis are the most common. A thorough and multidisciplinary approach to the severity of haemoptysis is essential to guide any therapeutic decision and its implementation. Vascular interventional radiology has become the first-line treatment of severe haemoptysis, with emergency surgical lung

resection being reserved for failure of endovascular treatment or focal lesions at high risk of recurrence. Therapeutic strategies based on knowledge of early prognostic factors should be developed to improve the prognosis of severe haemoptysis.

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Foreign body aspiration and inhalation injury

Erik H.F.M. van der Heijden[1], Paul C. Fuchs[2] and Jan-Philipp Stromps[2]

Foreign body aspiration is seen predominantly in children and elderly patients. Depending on the size, type and location of the foreign object, occlusion of the central airway can occur, resulting in life-threatening situations. Bronchoscopy is the cornerstone in the diagnosis and treatment of foreign body aspiration. Rigid bronchoscopy is preferred due to its larger lumen, allowing the use of more robust and larger tools and providing a secure airway during the procedure. In extreme cases, ECMO can be life-saving in children. The sooner the foreign body is removed, the less local inflammatory reaction occurs. The vast majority of foreign bodies can be retrieved by bronchoscopy. When unsuccessful, a thoracotomy may be needed. Inhalation injuries caused by smoke or chemical products of combustion are often associated with long-standing pulmonary dysfunction and significant morbidity and mortality. These traumas are often associated with skin burns, which increase the overall morbidity. Factors such as systemic inflammation, sepsis, ventilator-induced lung injury and post-traumatic development of pneumonia may also negatively affect the injured respiratory system. There is still no common consensus about the diagnostic strategy, and relatively few novel therapeutic options are available; therefore, treatments are for the most part supportive.

Foreign body aspiration is a globally widespread pulmonary emergency that may result in a life-threatening pulmonary emergency as result of an acute central airway obstruction. In children, especially in the case of unwitnessed (small) foreign body aspiration in the peripheral airways, a chronic clinical syndrome may develop, combining signs and symptoms of recurrent pneumonia, cough and wheezing. However, in this chapter, we will focus on the acute situation, discussing the clinical features of foreign body aspiration, and the emergency and initial general treatment of foreign body aspiration in children and adults.

Inhalation injuries are caused by smoke or chemical products of combustion. They are associated with significant morbidity and mortality, and often lead to long-term pulmonary dysfunction. It is recognised that a general consensus on treatment is needed. Here, we discuss the types and diagnosis of inhalation injuries and the available treatment options.

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Foreign body aspiration

Foreign body aspiration may result in a life-threatening pulmonary emergency as result of an acute central airway obstruction. It is essential that this clinical situation is recognised and that prompt and suitable action is undertaken. The incidence of foreign body aspiration is related to age, region and other factors, such as trends in clothing and games; it occurs most frequently in children and the elderly. The most frequently aspirated foreign bodies are peanuts, water melon seeds, hairpins and toy parts but also, in some regions, live organisms [1–11]. In adults, aspiration of food parts, medical devices, tooth fragments (resulting from trauma) and pills and other medication is more often reported (figure 1). Most of the available literature, and especially larger studies, have focused on children [12–14].

Clinical features

The presentation of foreign body aspiration depends on the size and nature of the foreign body. In general, the majority of patients with (suspected) foreign body aspiration present within 24 h [15, 16]. The presentation and acute risk depend on the relative size of the foreign body and the airway in which it is lodged (pharynx or central, upper or lower airway). Choking occurs when the foreign body is wedged in the retropharynx or central airway, and when witnessed it has a high predictive sensitivity for foreign body aspiration. However, whether the foreign body is (completely) expectorated after the often rapid

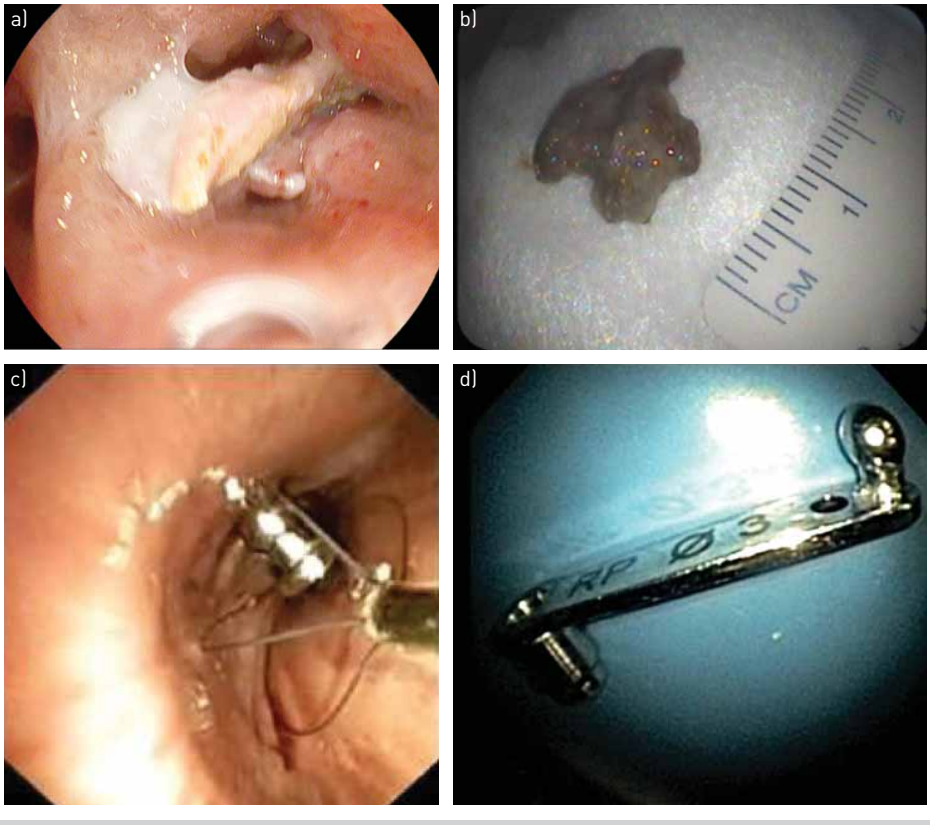

Figure 1. a and b) Bone fragment wedged in the anterior segment of the right lower lobe of the lung, and c and d) a surgical tool in the right lower lobe of the bronchus caught in a basket, before (a, c) and after (b, d) removal.

resolution of choking is uncertain. Often, after a period with few symptoms, a chronic syndrome may recur. The most frequently reported symptoms are cough, dyspnoea, tachypnoea, wheezing and stridor (table 1). Upon clinical examination, the combination of cough with diminished breath sounds, a hyperinflated lung, atelectasis and pneumonia is indicative of foreign body aspiration.

Most foreign bodies are aspirated in the right main and lower lobe bronchi due to their anatomical position [5, 12]. When the foreign body aspiration was unwitnessed or unnoticed, local inflammation may occur due to a chemical interaction, depending on the nature of the foreign body (*e.g.* pills, peanut oil) [13]. Granulation tissue formation may also mimic the symptoms of a pulmonary malignancy.

Imaging can be used in subacute situations in the diagnostic workup of foreign body aspiration and consists of a standard chest radiograph to reveal radio-opaque foreign bodies or to detect atelectasis or hyperinflation in radiolucent foreign bodies [2–5, 7, 12, 15, 16]. The sensitivity of CT scanning to detect foreign bodies is higher [17, 18].

Management of patients with foreign body aspiration

Prompt airway management is key in acute life-threatening foreign body aspiration. In these situations, it is critical that the airway is secured, and no time must be lost on, for example, imaging procedures. In children with asphyxia and complete airway obstruction (*i.e.* without the ability to speak), back blows, chest compression or the Heimlich manoeuvre can be attempted to dislodge the foreign body. In children who are able to speak or cough, these manoeuvres should be avoided outside the hospital (in a setting where the airway can be regained) to avoid complete blocking of the central airway [7, 15, 19]. Similarly, probing of the hypopharynx with a finger must be done with caution, since this may push a loose foreign body into the larynx, occluding the entire airway [15]. It is advised to retrieve foreign bodies in the hypopharynx with direct laryngoscopy and using Magill forceps.

Rigid bronchoscopy under general anaesthesia is the mainstay of foreign body aspiration treatment. The bronchoscope allows the passage of larger instruments and different types of graspers, allows the passage of the foreign body through the glottis and, most importantly, allows assisted or mechanical ventilation during the procedure. Furthermore, rigid bronchoscopy can easily be combined with flexible bronchoscopy to allow easy and complete

Table 1. Reported incidence of symptoms of foreign body (FB) aspiration

First author [ref.]	Subjects n	Symptom incidence			
		Cough	Stridor/wheezing	Tachypnoea/dyspnoea	Fever
Boufersaoui [2]	2624	70%	63%	60%	NR
Sahin [5]	1660	75%	14%	29%	8%
Huankang [3]					
Tracheal FB	146	96%	29%	12%	7%
Bronchial FB	843	98%	22%	7%	11%
Liang [4]	2000	33%	NR	55%	11%

NR: not reported.

examination of the peripheral airways. However, it is important that the referral centre has access to the full range of clinical expertise, since foreign body aspiration may still result in death, as occurs in approximately 0.3% of cases [2, 11], or in severe complications, with a rate of up to 9% of cases consisting of laryngeal oedema or spasm, hypoxaemia and pneumothorax [11]. Life-saving acute interventions other than rigid bronchoscopy include acute cricotracheotomy and ECMO in severe life-threatening cases [20–22] and surgical procedures such as bronchotomy carried out by a trained airway surgical team [2, 23].

In areas where rigid bronchoscopy is not available, or in the case of severe or unstable facial or cervical trauma, flexible bronchoscopy in combination with endotracheal intubation or laryngeal mask ventilation is an effective approach [12, 16]. Sometimes, tracheotomy may be a valuable alternative [24]. In the case of a history of choking or of prolonged symptoms, diagnostic flexible bronchoscopy can be used. It may be possible to remove the foreign body immediately; however, care must be taken not to lose the captured foreign body upon passing the glottis, and one should be prepared to maintain or regain a patent airway.

Foreign body retrieval is carried out under general anaesthesia. Different techniques are used and are subject to local preference, and it should be noted that, in an acute situation, the patient may have a full stomach [25]. Often, spontaneous breathing is preferred over controlled ventilation [26] and isoflurane over the combination of intravenous propofol and remifentanil [25, 27–29]. However, since rigid bronchoscopy is essentially an open airway procedure, intravenous sedatives are preferred to avoid ambient fumes. In general, local protocol preference seems the most important factor.

Several tools are available for the retrieval of foreign bodies using both rigid and flexible bronchoscopy. A variety of accessories including specially designed forceps, snares, baskets, balloons and magnets can be used during rigid and flexible bronchoscopy for foreign body extraction. Cryoprobes can also be used to freeze organic material onto the tip of the cryoprobe and retract the foreign body [12], similar to ablative therapy used for airway recanalisation in malignant central airway obstruction. Cryotherapy as well as electrocautery or laser therapy may be needed to remove granulation tissue around foreign bodies that have been *in situ* for a longer period. When the foreign body is located in segmental bronchi, it may be difficult to reach with a rigid bronchoscope. In such cases, flexible bronchoscopy can be used through the rigid bronchoscope. An important limitation in the use of flexible bronchoscopes in children is the size of the outer diameter of the bronchoscope and its working channel diameter. Adult therapeutic videobronchoscopes are available with 2.8 mm or 3.2 mm working channels and allow the use of a wide range of accessories. For narrower bronchoscopes, the working channel is 2.0 mm, and for ultrathin bronchoscopes with an outer diameter of <4 mm, the working channel is 1.2 mm. Such ultrathin bronchoscopes with these small working channels allow the use of baskets and can also be used to position guide wires past the foreign body over which a retraction balloon can be inserted to retract the foreign body under vision into the rigid bronchoscope or a larger airway where it can be retrieved using larger instruments or accessories. It is strongly advised that a wide variety of these tools and accessories is available for immediate use in centres for interventional pulmonology. Special expertise and dedicated experience is needed for the successful removal of living foreign bodies, such as leeches or fish [6, 9].

In the rare case when the foreign body cannot be removed from the airways, surgeons trained in airway surgery must be consulted. In a large retrospective study, surgery was found to be needed in only 3% of cases where (rigid) bronchoscopy was unsuccessful [2].

Thoracotomy is often preferred over video-assisted techniques to allow bronchotomy or lobectomy to remove the foreign body [23, 30, 31].

Inhalation injury

Injuries of the respiratory system caused by inhalation of smoke or chemical products of combustion are often associated with long-standing pulmonary dysfunction and significant morbidity and mortality [32, 33]. In combination with burns, inhalation injury leads to an increased overall mortality from thermal injury [34]. In critically ill patients in particular, other factors such as systemic inflammation, sepsis and ventilator-induced lung injury may also negatively affect the injured respiratory system [35]. Another problem is the post-traumatic development of pneumonia during hospitalisation. The need for a common consensus on diagnostic strategy has been recognised in the burn literature over the last few decades. Relatively few novel therapeutic options are available and treatment concepts are for the most part supportive [36].

Anatomy and physiology

Inhalation injury is defined as trauma to the respiratory system caused by either thermal or chemical irritants. These traumas can be divided into three categories: 1) heat injuries to the upper airways; 2) chemical irritation to the lower airways; and 3) systemic toxicity.

Heat injuries to the upper airways

Injuries to the upper airways are commonly caused by heated air, which can reach >500°C in a burning room. Due to the reflex closure of the larynx, these injuries are limited to the structures above the carina. Inhalation can lead directly to massive swelling of the tongue and epiglottitis, resulting in severe obstruction of the upper respiratory tract.

Chemical irritation to the lower airways

Toxic products of combustion (table 2) mainly affect the epithelial and capillary endothelial cells of the lower respiratory tract. Damage to these cells leads to a lower surfactant level, which further promotes alveolar collapse and atelectasis. An early inflammatory response by excretion of mediators such as interleukins and tumour necrosis factor-α is initiated mainly through the alveolar macrophages [37]. Mucociliary transport is constrained and therefore bacterial clearance is reduced, leading to the development of additive pneumonia. A summary of the complex relationships that occur following inhalation of toxic gases is shown in figure 2.

Table 2. Examples of toxic products of combustion

Sulphur dioxide
Nitrogen dioxide
Ammonia
Chlorine
Cyanide
Various toxic aldehydes and acids

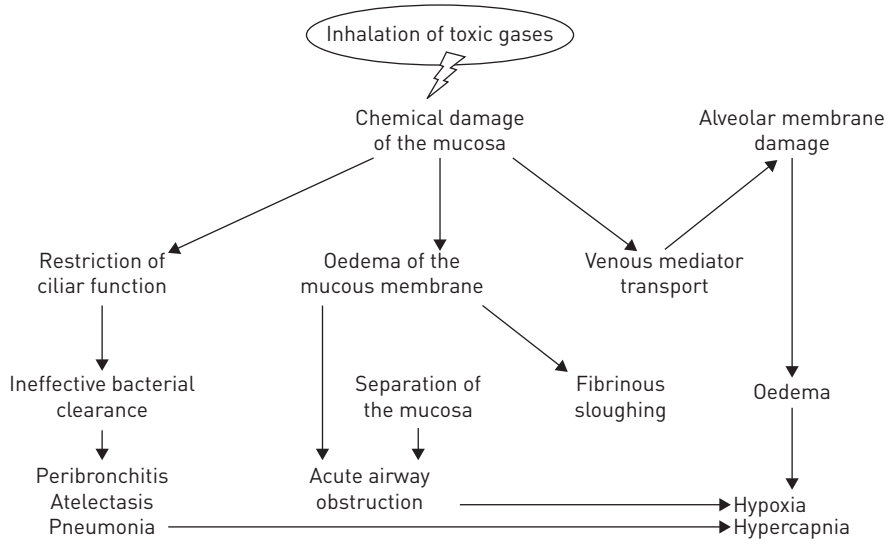

Figure 2. The complex relationships after inhalation of toxic gases.

Systemic toxicity

Apart from the systemic inflammatory reaction after inhalation injury, systemic toxicity is tied mainly to high levels of carbon monoxide, which is a product of incomplete combustion during fires. The main risk of this tasteless and odourless gas is that it competes with oxygen for haemoglobin binding. The binding capacity of carbon monoxide is 200–250-fold greater than that of oxygen, which leads to higher carboxyhaemoglobin levels, resulting in reduced overall oxygen saturation of the patient. Long-term morbidity due to carbon monoxide intoxication includes vascular and neurological consequences.

Diagnosis of inhalation injury

The diagnosis of inhalation injuries is often based on the patient's history of smoke exposure and on critical symptoms such as unconsciousness. The most common clinical symptoms are listed in table 3. These symptoms may not be proportional to the degree of smoke exposure or injury.

The clinical course of inhalation injury can be divided into three phases according to Herndon *et al.* [38]: 1) the early phase, which is determined by reduced oxygenation and acute alveolar lung oedema; 2) the following intermediate phase (from 6 h up to 72 h

Table 3. Clinical symptoms of acute inhalation injury

Swelling of the tongue
Irritated throat and sinuses
Obstruction of the airways and coughing
Vomiting and nausea
Shortness of breath
Chest pain
Headaches
Stinging eyes

post-trauma), with increased excretion and decreased clearance within the injured lung leading to atelectasis and an interstitial oedema; and 3) the late phase (beginning 7 days after trauma), described by further obstruction and fibrin formation and the possible development of pneumonia, which can result in the development of ARDS.

Diagnostic strategies include fibreoptic bronchoscopy, with the possibility of investigating the bronchoalveolar lavage fluid [39, 40]. Various scoring systems have been proposed to estimate the severity of the injury to the respiratory tract and estimate the further clinical course; these are based on the bronchoscopic findings, which can range from mild erythema and carbonaceous deposits up to mucosal necrosis [40, 41]. Various diagnostic tools have been developed to determine carbon monoxide intoxication, but they are very unpredictable since the level of initial carbon monoxide does not correlate with the outcome [42, 43].

In general, it is difficult to predict pulmonary dysfunction, the development of ARDS and overall mortality, since these reactions are orchestrated and influenced by many different factors. The clinical use of other diagnostic tools, such as lung scanning with xenon or technetium-99, is limited due to logistical reasons [44].

Therefore, a diagnosis determined by clinical findings and bronchoscopy should be considered in clinical practice [36].

Treatment of inhalation injury

Patients suffering an inhalation injury need special treatment concepts. The therapeutic options include the following, depending on the individual severity of injury: fluid resuscitation, bronchoscopy, hyperbaric oxygen treatment, mechanical ventilation and specific agents for treating inhalation injury.

Fluid resuscitation

Patients with inhalation injuries usually require high volumes of fluid during immediate resuscitation [40, 45]. When there is a concomitant burn injury, the Parkland formula (4 $mL \cdot kg^{-1}$ bodyweight per % burned body surface area) is merely used to calculate the basic fluid requirements within the first 24 h after trauma.

The individual fluid requirements should be adjusted according to the haemodynamic stability and the hourly urine output, which should not be <1 $mL \cdot kg^{-1}$ bodyweight [46].

Bronchoscopy

As well as its diagnostic value, bronchoscopy also provides therapeutic options, such as clearing the respiratory tract of obstructions caused by carbonaceous deposits, sloughed epithelial cells, mucus and fibrin formations.

Hyperbaric oxygen treatment

To reduce the negative influence of carbon monoxide and accelerate its displacement from haemoglobin, hyperbaric oxygen (HBO) can be used if logistically available. The half-life of haemoglobin can be reduced to <60 min by inhalation of 100% oxygen, compared with 240 min under normal oxygen saturation. Although many studies and clinical trials suggest a positive effect of HBO treatment, its use remains controversial [47]. Complications associated with HBO treatment include barotrauma and air embolism.

Mechanical ventilation

If necessary, ventilation and oxygenation can be enhanced by noninvasive and invasive treatment modalities. Since it is difficult to evaluate the severity of obstruction and lung damage directly after trauma, intubation for airway protection must always be considered. The benefits of NIV are associated mainly with avoidance of the complications of endotracheal intubation. These include the trauma during intubation, the need for higher sedation levels, and impaired communication and swallowing after extubation. Unconscious patients generally require intubation and invasive ventilation.

The use of PEEP has been proven to enhance arterial oxygenation by increasing functional residual capacity, especially in patients with ARDS [48]. The use of ventilator strategies, which induce hypercapnia by limitation of minute ventilation by using low tidal volumes, has been controversially discussed [49].

Agents for treating inhalation injury

There are different specific antidotes available to combat the toxic products of combustion, but most of these drugs, which can be additionally administered, reduce the inflammatory response and address the physiological changes; they have been the focus of many animal models. The use of antibiotics should be limited to cases of documented infection and pneumonia.

Some studies have shown reduced mortality in patients following inhalation injury by using a combination of aerosolised heparin/*N*-acetylcysteine, but their widespread use remains controversial [50, 51]. In this context, the use of nebulised inhaled β-agonists has been proven to ameliorate bronchoconstriction and thus lead to enhanced gas exchange in various animal studies [52, 53]. Another target of studies is changing the pulmonary blood flow through vasodilatation by inhalation of nitric oxide [54, 55].

Conclusion

Foreign body aspiration and inhalation injuries can be life-threatening situations for which immediate and prompt action is warranted. In case of central airway occlusion, Heimlich manoeuvres or back blows should be avoided in choking patients with the ability to cough or speak. Most often, the foreign body is aspirated in the main bronchi and predominantly in the right main or lower lobe bronchus. Bronchoscopic retrieval of the foreign body is indicated, preferably by means of rigid bronchoscopy. A wide variety of accessory tools is available for the complete retrieval of different foreign bodies. In emergency cases, it is critical to secure the airway, and in exceptional cases this may involve an emergency tracheostomy, ECMO or surgery.

The diagnosis of inhalation injuries is often based on the patient's history of smoke exposure and on critical symptoms such as unconsciousness. Bronchoscopy should be performed not only for diagnostic reasons but also for therapeutic options, such as clearing the respiratory system. Fluid resuscitation is also mandatory within the early phase following these injuries. Intubation for airway protection should always be considered, since it is difficult to evaluate the severity of obstruction and lung damage directly after inhalation traumas. If necessary, ventilation and oxygenation can be enhanced by noninvasive and invasive treatment modalities, or even HBO treatment. Additionally, drugs can be administered to reduce the inflammatory response, but the use of antibiotics should be limited to cases of documented infection and pneumonia.

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Haematothorax

Erich Stoelben[1], Axel Gossmann[2] and Servet Bölükbas[3]

Haematothorax (or haemothorax) is defined as an accumulation of blood in the pleural cavity. Spontaneous haematothorax is a rare complication of various intrathoracic diseases, especially pneumothorax or benign and malignant neoplasms. In contrast, haematothorax has to be faced regularly after thoracic interventions due to the high number of interventional procedures in the thorax, especially thoracentesis or thoracic drainage. Diagnosis has to be made by means of the clinical picture, sonography and CT scan of the chest. Spontaneous or post-interventional haematothorax might turn out to be an emergency situation requiring immediate interdisciplinary treatment. Depending on the underlying cause, conservative and surgical treatment might be appropriate. However, early video-assisted thoracic surgery is an effective and safe treatment for the management of haematothorax irrespective of the underlying disease.

Haematothorax (or haemothorax) is defined as an accumulation of blood in the pleural cavity. This chapter focuses on patients with spontaneous haematothorax or intrapleural bleeding after medical interventions. Post-interventional haematothorax is a clinical emergency that requires rapid treatment and close cooperation of the primary attending physician, the radiologist and the respiratory specialists in pneumological and thoracic surgery.

The PubMed literature was searched for haemo- or haematothorax (and spelling variations thereof). Literature concerning post-operative, post-traumatic and in context with aortic aneurysm-treated haematothorax was excluded. If appropriate, well-written reviews are cited in this chapter in order to limit the number of case reports in the list of references. The recommendations given here are mainly based on clinical case series, case reports and the clinical experience of the authors. They are not supported by prospective randomised studies.

Definition criterion and clinical presentation

Pleural effusion is common and has to be distinguished from haemorrhagic exudate and haematothorax. In a visual examination, a content of 5% haematocrit makes the effusion indistinguishable from blood.

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A haematocrit in the punctate of at least 50% of the haematocrit in the patient's blood is postulated for the definition of haematothorax [1, 2]. However, the haematocrit in the punctate should be interpreted with caution. The process of coagulation binds the red cells, leaving a fluid supernatant with a low content of erythrocytes. Therefore, the criterion for the definition of haematothorax is not always really helpful.

The patient should be treated in the same way as an emergency for haematothorax and haemorrhagic pleural effusion and whenever coagulated or solid masses with the pleural effusion are detected by sonography and/or a CT scan of the chest. In cases of previous intervention, the cause of the haematothorax is obvious. Otherwise, such as in rare spontaneous haematothorax, the history of the patient may give some suggestions. Nonetheless, diagnosis can be challenging.

The intrathoracic accumulation of blood leads to chest pain, dyspnoea and cough. Patients might compensate for the loss of intravascular volume by vasoconstriction. In this case, the clinical sign might be a cold white nose. If bleeding persists and compensation mechanisms such as dilution of blood from the interstitial space are overstressed (*i.e.* leading to a fall in haematocrit), the blood pressure decreases and the heart rate rises. This may result in a positive shock index (heart rate (beats·min^{-1})/systolic blood pressure (mmHg)). Furthermore, the accumulation of large amounts of fluid in the thoracic cavity can lead to respiratory stress with elevated breathing frequency. Now the patient is in a life-threatening situation and needs effective help by volume resuscitation and interventions to stop the bleeding. Intrathoracic bleeding is regularly underestimated, as the bleeding is not visible and the pleural cavity on one side comprises a volume of ~3–6 L. Therefore, the primary task of the attending physician is to prevent the patient reaching the life-threatening stage of intrapleural bleeding.

Causes and epidemiology

Haematothorax is a rare event except in traumatic and post-interventional situations. As we do not have access to epidemiological data, we are forced to cite case series, which carry the risk of selection bias. On this basis, we can quantify the risk of haematopneumothorax to be 3–5% of all pneumothorax cases and the risk of haematothorax in patients with hereditary haemorrhagic telangiectasia to be 3–5% of the patients with this disease. Only a small number of case reports have been published for all other causes of spontaneous haematothorax and this does not allow an estimation of the incidence (table 1).

Spontaneous haematothorax

Haematopneumothorax

In patients with pneumothorax, concomitant haematothorax can occur in 3–5% of the patients because a solitary apical adhesion bearing a small interpleural artery ruptures due to the lung collapsing (figure 1).

The artery has developed following inflammatory adhesions and does not contain normal structures such as smooth muscle cells. Therefore, the bleeding can persist, requiring emergency surgical intervention in about one-third of patients [3, 4, 23]. A current epidemiological study on the incidence of pneumothorax in France [24] confirmed a rate of 22.7 spontaneous pneumothoraxes per 100 000 population per year with a female/male ratio of 1:3.3. Therefore, haematopneumothorax may be a relevant clinical setting in young males.

Table 1. Causes and incidences of haematothorax

Cause	Incidence	Reference(s)
Spontaneous		
Haematopneumothorax	3–5% of patients with pneumothorax	[3, 4]
Hereditary haemorrhagic telangiectasia	3–5% of patients with hereditary haemorrhagic telangiectasia	[5, 6]
Malignant tumours of the lung or pleura	Case reports	[7]
von Recklinghausen disease/ schwannoma	Case reports	[1, 7–9]
Multiple exostosis	Case reports	[1, 7]
Anticoagulation and coagulation disorders	Case reports	[7]
Endometriosis	Case series	[10–12]
Extramedullary haematopoiesis	Case reports	[1, 7, 13]
Vascular aneurysm (Ehlers–Danlos syndrome)	Case reports	[14, 15]
Post-interventional		
Central venous catheter	<0.5%	[16, 17]
CT-guided lung biopsy	1–3.5%	[18, 19]
Thoracic drainage	0.2–1.4% (depending on size of drainage)	[20]
Thoracentesis	0–1%	[21, 22]

Hereditary haemorrhagic telangiectasia

The cause of haematothorax is not known. One explanation might be a superficial pulmonary arteriovenous malformation rupturing and bleeding into the pleural space. In the published case series, the diagnosis of hereditary haemorrhagic telangiectasia was made after the third decade of life in most of the patients. The prevalence of hereditary haemorrhagic telangiectasia is estimated to be between 1 per 5000 and 1 per 10 000 population [5, 6]. In the case of spontaneous haematothorax, the CT scan should be checked for pulmonary arteriovenous malformation and telangiectasia of the lips and the mucosa.

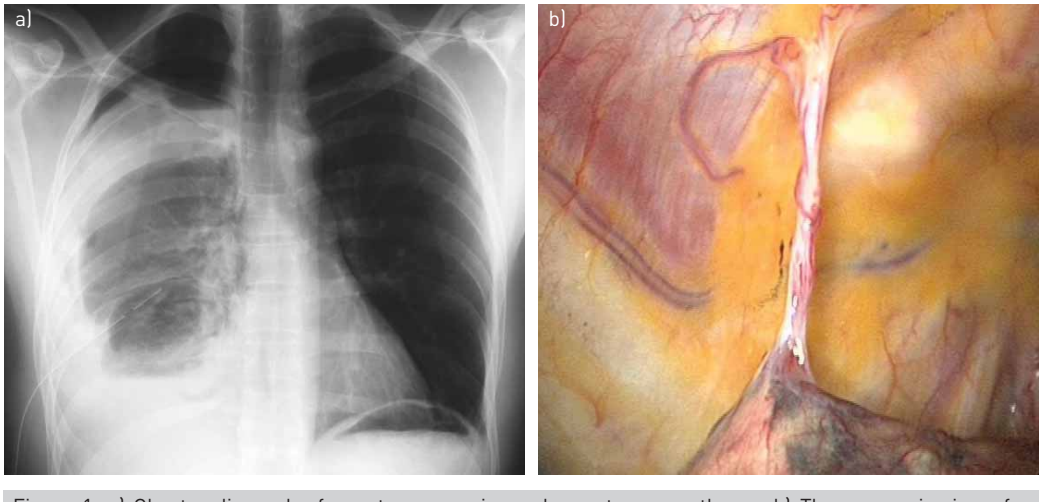

Figure 1. a) Chest radiograph of spontaneous primary haematopneumothorax. b) Thoracoscopic view of a solitary apical adhesion.

Malignant tumours

Haematothorax can be generated by intrapulmonary tumours such as lung cancer or pulmonary metastases penetrating the visceral pleura, or by tumour spread in the interpleural space. Furthermore, tumours from the mediastinum, chest wall or subdiaphragmatic space can lead to intrathoracic bleeding. Highly vascularised malignancies such as angiosarcoma [25], renal cell carcinoma (experience of the authors) or hepatocellular cancer [1] as the cause of haematothorax are published in small series. Overall, the risk of bleeding is low considering the high number of intrathoracic primary and secondary tumours. In most cases, haematothorax indicates an advanced tumour stage and a very limited prognosis (figure 2).

Von Recklinghausen disease/schwannoma

Small case series with haematothorax have been analysed in patients with von Recklinghausen disease and/or schwannoma. In some patients, bleeding was associated with the local growth and complication of a schwannoma. Indeed, resection of a schwannoma (figure 3) can be bloody, this being caused by peritumoural hypertrophied intercostal vessels. In other patients, rupture of a subclavian or intercostal artery showing histopathological signs of dysplasia was the cause of bleeding [1, 8, 9, 26].

Coagulopathy

Bleeding in the thoracic cavity under anticoagulation or in patients with congenital or acquired coagulopathy is extremely rare without an underlying intrathoracic disease [1]. However, in the case of pleural disease, which can cause haematothorax, coagulopathy may aggravate bleeding and complications.

Endometriosis

Endometriosis is a relatively common disease in pre-menopausal women (5–15%). The catamenial thoracic symptoms of thoracic endometriosis are a rare manifestation of the disease, and comprise pneumothorax, haemoptysis and haematothorax. The right side of the thorax is affected in 80% of cases. The symptoms are recurrent. Haematothorax occurs in 8–15% of patients with thoracic endometriosis and is associated with the pleural implants

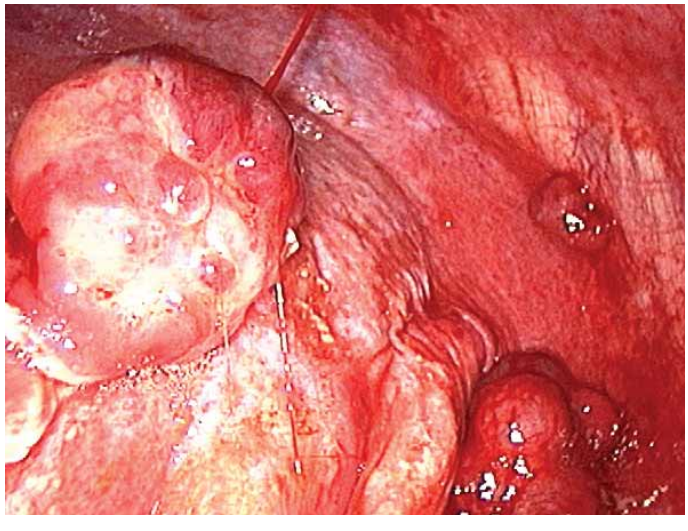

Figure 2. Thoracoscopic view of pleural carcinosis from a renal cell carcinoma.

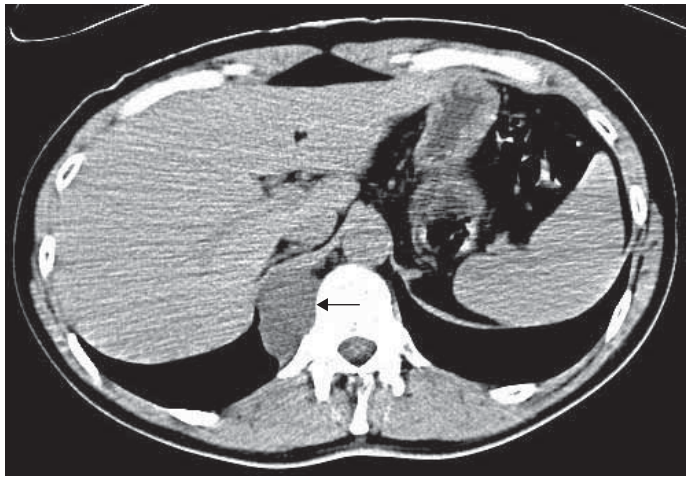

Figure 3. CT scan of neoplasm of the posterior mediastinum: schwannoma.

of endometriosis [10–12]. Treatment requires the cooperation of gynaecological and thoracic surgery with local and systemic interventions.

Others

Diseases such as extramedullary haematopoiesis [13], vascular-type Ehlers–Danlos syndrome [14, 15], (multiple) exostosis of the ribs [1, 7] and rare vascular aneurysm [27] can also be complicated by haematothorax. The number of published cases is below 20 for each entity.

Haematothorax after medical intervention

Central venous catheterisation

The procedure is routine in anaesthesia, intensive care medicine, oncology and other medical specialities. Most papers focus on pneumothorax or infection after catheter placement. The risk of haematothorax is low [16, 17]. The main cause of bleeding is puncture of the accompanying artery (carotid or subclavian artery). A non-self-limiting haematoma can disrupt the mediastinal pleura or the needle can perforate the artery and the pleura with direct bleeding into the pleural space. In our experience, the risk of clinically relevant haematothorax is elevated in patients with antiplatelet medication and other coagulation disorders. Treatment can be demanding, as the exact localisation of the injury of the artery in a sometimes extended haematoma in the upper sulcus of the thorax or supraclavicular region can be difficult.

CT-guided biopsy

CT-guided biopsies are regularly used to confirm the histology or stage of lung tumours. The main complications are pneumothorax and intraparenchymal bleeding with haemoptysis. The overall rate of complications is ~30%. Between 6% and 10% of patients need therapy, mainly thoracic drainage. The risk of haematothorax is 1–3.5%; none of the patients studied needed an intervention [18, 19].

Thoracic drainage

This procedure is used for the therapy of pneumothorax or pleural effusion, including haematothorax and pleural empyema. The rate of adverse events depends on the

circumstances involved (emergency, experience of the physician), method of application, diameter of drainage and underlying disease, including coagulation disorders [20, 28]. The source of bleeding can be the intercostal artery (figure 4), the lungs and all other organs in or around the thoracic cavity. The use of large-bore trocar drainage bears the highest risk of bleeding. The safest way to treat the patient is the use of small-bore drainages (9–14 French) in combination with sonography and the Seldinger technique. As in thoracentesis, impaired coagulation is not an absolute contraindication for drainage.

Thoracentesis

The indication for thoracentesis is sometimes liberal. Although the rate of pneumothorax (2–6%) and haematothorax (<1%) is low, the bleeding complications in patients with cardiovascular disease and antiplatelet therapy can be life threatening. Injury to the intercostal artery or a diaphragm vessel can remain undetected until a patient develops signs of hypovolaemia. However, correction of coagulopathy does not decrease the risk of bleeding [18, 20–22].

Diagnosis

Spontaneous haematothorax

In patients with spontaneous haematothorax, the clinical signs of chest pain, including pain in the upper abdomen, cough and dyspnoea, initiate a routine check-up involving chest radiography and/or sonography. In experienced hands, sonography might give the same or even more information than a chest radiograph. The echo image of the fluid can provide important suggestions for the differentiation between uncomplicated pleural effusion, pleural empyema or haematothorax. Sonography is performed more quickly and is always available [20, 29]. It should be kept in mind that the studies on the use of sonography in haematothorax were mainly conducted on trauma patients. The patient's history has to be checked for the above-mentioned conditions, including coagulopathies.

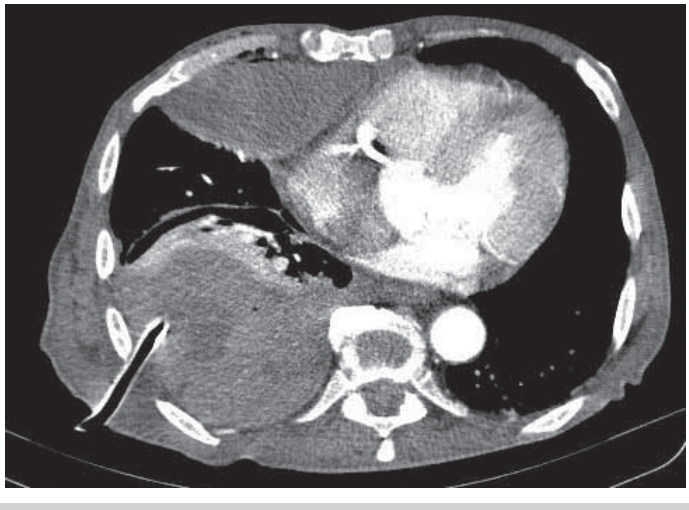

Figure 4. CT of the chest demonstrating haematothorax after trocar chest tube placement.

If haematothorax is suspected, a CT scan is indicated to identify the cause, extent and source of bleeding. This information is important to plan further treatment. Simultaneously, laboratory tests, including blood group determination, should be initiated.

The diagnostic step has to be cancelled if the patient presents with signs of cardiorespiratory and circulatory insufficiency. Therapy with volume resuscitation and thoracic drainage (minimum 24 French) must start immediately and a blood transfusion has to be prepared. In the case of massive haematothorax of >1500 mL or persistent bleeding of >200 $mL \cdot h^{-1}$, patients have to be operated on immediately. This approach is recommended in nearly all studies for patients with haematothorax of variable causes without any compelling evidence [2, 30].

Haematothorax after medical intervention

After the thoracic interventions detailed earlier, the attending physician has to organise appropriate clinical and/or imaging follow-up. If pleural effusion occurs within 24 h, haematothorax is likely. The bleeding source is predetermined by the intervention and intervention site. Therefore, a CT scan is not always necessary. In stable patients, thoracic drainage and correction of an underlying coagulopathy is the first step of diagnosis and therapy. In unstable patients, or in the case of massive haematothorax or persistent bleeding, the same procedure has to be used as in patients with spontaneous haematothorax (see the later section on surgical treatment).

Treatment

Conservative treatment

In stable patients with spontaneous or post-interventional haematothorax, initial treatment consists of a thoracic drainage of 24–36 French, which has to be placed following standardised guidelines [20].

We do not know in which and in how many patients drainage and correction of coagulopathy solve the problem by stopping the bleeding. Furthermore, there is a risk of retained haematothorax. The coagulated blood cannot always be drained completely, and this leads to the risk of pleural empyema, recurrent pleural effusion and fibrothorax. Once again, these risks have been well studied in trauma patients with haematothorax, but detailed evidence-based data for the patients discussed here are not available.

Importantly, about one-third of the patients with haematopneumothorax have to be operated on for massive haematothorax or persistent bleeding. Most of the remaining patients need a secondary surgical intervention for retained haematothorax or persistent pneumothorax using a minimally invasive, video-assisted thoracoscopic surgery (VATS) procedure. Therefore, a primary surgical procedure is recommended for most of the patients [4]. However, the application of fibrinolytic agents (urokinase, streptokinase and tissue plasminogen activator) was performed with a success rate of ~80% [31–33]. Unfortunately, the number of studies is small and the quality low. The time point of application, dose, agent and number of applications are not well defined.

Bleeding from injury to the intercostal or mammary artery or from a ruptured aneurysm can be treated by interventional radiology and application of coils by means of bronchial artery embolisation (figure 5) [27, 34].

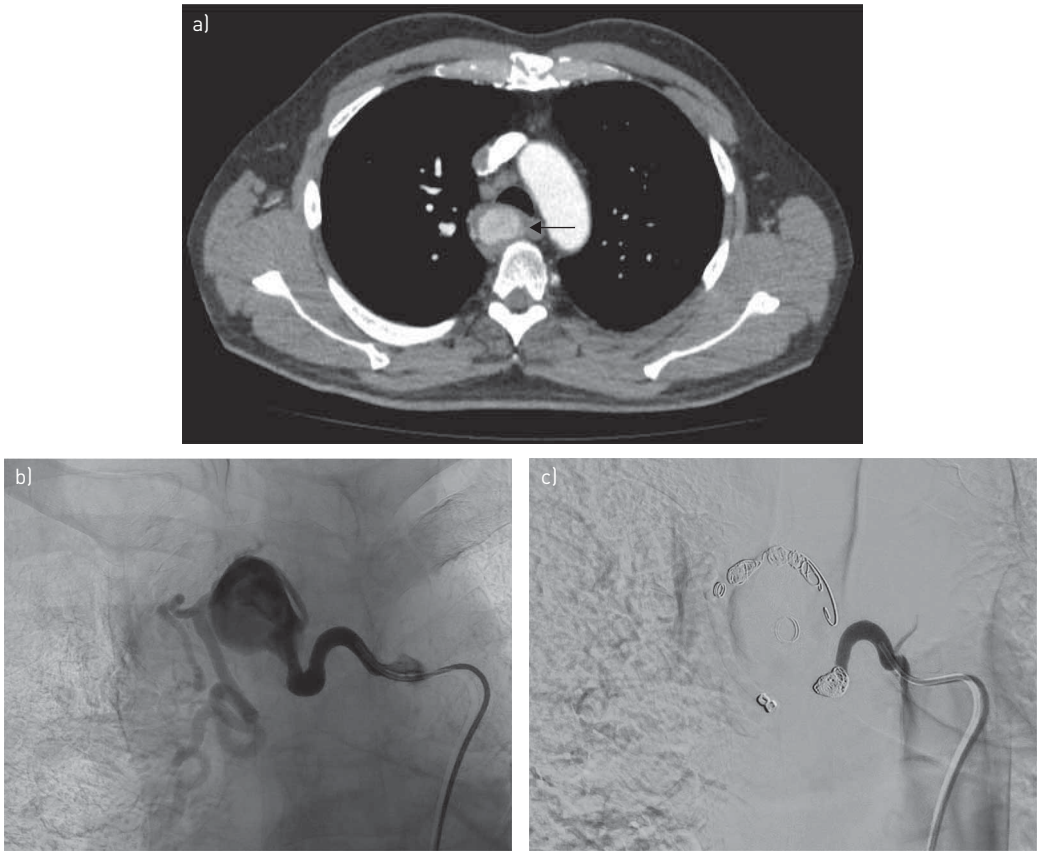

Figure 5. Sarcoidosis of the mediastinal lymph nodes and aneurysm of a bronchial artery in the mediastinum. a) CT of the chest with contrast enhancement, b) angiography and c) embolisation.

Immediate treatment is required in unstable patients. We discussed the emergency procedure in the earlier section on diagnosis (figure 6).

Surgical treatment

Following medical intervention or persistent bleeding in spontaneous haematothorax, the surgeon could plan the intervention depending on a CT scan, the anatomical situation and the underlying disease. Thoracic surgery is turning more and more to minimally invasive surgery, ranging from diagnostic procedures to complex anatomical resections and interventions. Therefore, in experienced hands, minimally invasive, video-assisted access could be used safely and effectively to control bleeding in most cases and to evacuate the coagulated blood [2, 30].

In the case of retained haematothorax, the evacuation of the clotted blood should be performed as early as possible before organisation starts, preferably within 1 week [7, 30, 35]. In patients who are not candidates for surgery, the local application of fibrinolytic agents might be an alternative.

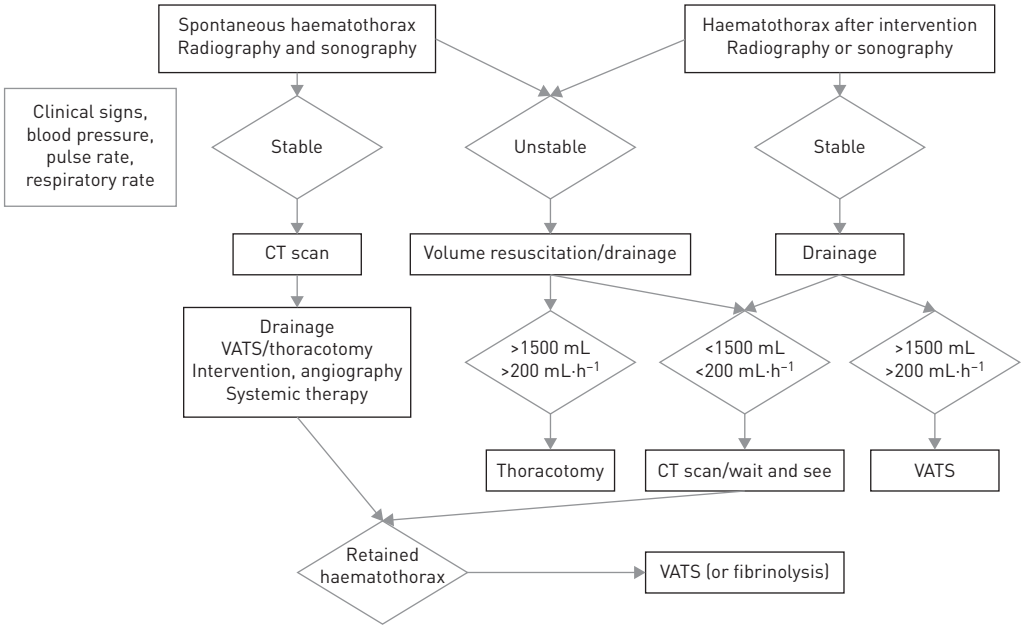

Figure 6. Haematothorax treatment strategy algorithm. VATS: video-assisted thoracoscopic surgery.

The most challenging situation for the thoracic surgeon may be the unstable patient with spontaneous haematothorax without a CT scan. The surgeon has to face a number of causes and sources of bleeding. In this situation, emergency thoracotomy enables the broadest spectrum of interventions. Otherwise, and in the case of massive bleeding, thoracotomy is the access of choice anyway.

Conclusions

Haematothorax is a rare event except in traumatic and post-interventional situations. Haematothorax has to be distinguished from haemorrhagic exudate and pleural effusion. Spontaneous or post-interventional haematothorax might turn out to be an emergency situation requiring immediate interdisciplinary treatment. Depending on the underlying cause, conservative and surgical treatment might be appropriate. However, early VATS is an effective and safe treatment for the management of haematothorax irrespective of the underlying disease. Thoracotomy should be used in unstable patients with unknown cause of bleeding.

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High-flow nasal cannula oxygen therapy

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High-flow nasal cannula (HFNC) oxygen therapy is a recent technique enabling delivery of a high flow rate of gas heated and humidified as under physiological conditions. The main clinical effects include a significant decrease in respiratory rate, work of breathing, and patient discomfort and breathlessness as compared with standard oxygen. These effects are mainly due to the high flow rate of gas that effectively matches the high ventilatory demand in patients, and provides high F_{IO_2}, PEEP and continuous washing of dead space, thereby flushing carbon dioxide out of the upper airways. Several RCTs have compared HFNC oxygen *versus* standard oxygen or NIV. In keeping with this literature, the use of HFNC oxygen could be the first-line strategy of oxygenation in patients admitted to the ICU with acute hypoxaemic respiratory failure, during the post-extubation period or after cardiac surgery.

The use of standard oxygen through a reservoir mask has long been the first-line therapy of choice in patients with acute respiratory failure (ARF). However, this strategy is far from ideal. Indeed, it does not reduce the work of breathing and/or improve alveolar ventilation, and F_{IO_2} delivered to the patient does not exceed 70%, even with a flow rate of 15 L·min^{-1}. Moreover, the oxygen provided by a hospital outlet or by a tank is a particularly dry gas that may irritate the airways, alter mucociliary clearance and cause discomfort for the patient.

The use of NIV is the main alternative to standard oxygen in patients with ARF. The gas delivered to the patient can be heated and humidified, with a F_{IO_2} close to 100% in the absence of leaks, and provide positive pressure which improves gas exchange and reduces patient inspiratory effort. However, good tolerance to NIV is sometimes difficult to achieve due to frequent leaks around the mask, often leading to patient–ventilator asynchronies. Moreover, some deleterious effects may occur with NIV, such as delayed intubation by masking signs of respiratory distress or potential barotrauma provoked by the high tidal volumes that can occur with pressure support ventilation.

High-flow nasal cannula (HFNC) oxygen therapy is a more recent oxygenation technique enabling delivery of high F_{IO_2}. Although there is no pressure support, the high flow

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generates low levels of PEEP and provides continuous washout of dead space in the airways. These physiological effects may help to improve gas exchange, and to reduce respiratory rate and patient effort, without increased risk of barotrauma. This oxygenation strategy seems particularly comfortable for the patient thanks to nasal cannulae ("prongs") delivering a warmed and humidified gas similar to physiological conditions, and allowing the patient to continue drinking and eating. The use of HFNC oxygen therapy is growing, and we focus our chapter first on physiological aspects to understand its clinical effects and then on clinical evidence for its use in clinical practice.

Characteristics and physiological effects of HFNC oxygen therapy

Physiological effects of HFNC oxygen therapy are due to 1) the warming and humidification of gas delivered through nasal cannulae, and 2) the high flow rate.

Warming and humidification of delivered gas

Under physiological conditions, and regardless of the external environment, the inspired gas needs to be heated and humidified in the airways to reach the alveoli with a temperature of 37 °C and containing 44 $mg \cdot L^{-1}$ of water, *i.e.* completely saturated with water (relative humidity of 100%). Oxygen delivered from a hospital outlet or from a tank is a particularly cold and dry gas with humidity <5 $mg \cdot L^{-1}$ of water [1], which could irritate and increase the resistance of the airways [2]. HFNC oxygen is delivered *via* a heated humidifier and it has been shown that it significantly decreases the sensation of airway dryness as compared with standard oxygen [3–5]. Warming and humidification of oxygen possibly help to decrease patient discomfort and a sensation of dyspnoea observed when switching from standard oxygen to HFNC oxygen [5, 6]. Whether or not heating and humidification of inspired gases may prevent thick secretions and subsequent atelectasis is an unproven hypothesis.

Mismatch between the patient's inspiratory flow rate and oxygen flow rate: impact of high flow on F_{IO_2}

Although F_{IO_2} delivered to the patient can reach up to 100% when using NIV in the absence of leaks, maximal F_{IO_2} does not exceed 70% with standard oxygen despite a reservoir mask and a flow rate up to 15 $L \cdot min^{-1}$ [6, 7]. Indeed, the inspiratory flow rate generated by a patient suffering from ARF reaches at least 30–40 $L \cdot min^{-1}$ on average, and can even exceed 60 $L \cdot min^{-1}$ in more severe patients [8], which is markedly higher than the flow rate delivered with standard oxygen. Oxygen is consequently mixed with room air, reducing F_{IO_2} delivered to the patient. In a physiological study, Sim *et al.* [7] measured F_{IO_2} in healthy subjects ventilated using a standard mask, a non-rebreathing mask with a reservoir and HFNC oxygen. Using a standard mask, F_{IO_2} was <60% despite a flow rate of 12 $L \cdot min^{-1}$ and dropped to <50% when they simulated ARF by thoracic contention. Although the non-rebreathing mask avoided such a drop of F_{IO_2} during ARF, F_{IO_2} was <70% even with a flow rate of 15 $L \cdot min^{-1}$. By comparison, F_{IO_2} reached 85% using HFNC oxygen set with a flow rate of 40 $L \cdot min^{-1}$. This effect could directly contribute to improvement in oxygenation and to the decrease in the respiratory rate observed when switching from standard oxygen to HFNC oxygen.

Positive pressure generated by high gas flow rate

The use of HFNC oxygen could generate PEEP directly proportional to the gas flow delivered: the higher the flow, the higher the pressure. The large nasal cannulae could create a certain degree of nasal obstruction while the continuously delivered high flow causes resistance during expiration, thereby generating positive pressure. Consequently, this PEEP effect is markedly reduced when the patient opens his/her mouth. PARKE *et al.* [9] measured nasopharyngeal pressure in patients at different levels of flow using HFNC delivery. The PEEP level exceeded 3 cmH_2O with a gas flow rate of 50 $L{\cdot}min^{-1}$ and with a closed mouth, whereas it dropped to <2 cmH_2O with an open mouth. Although the PEEP level seems only moderate, this PEEP effect could help to improve gas exchange and decrease the work of breathing in patients, as with CPAP in patients with intrinsic PEEP [10]. In a physiological study that measured pulmonary volumes after cardiac surgery using inductance plethysmography, an increase in end-expiratory lung volume was found with HFNC oxygen therapy, suggesting alveolar recruitment induced by this PEEP effect [11].

Washout of dead space in the airways induced by high gas flow rate

The high flow rate of gas continuously delivered in the airways may generate a washout of dead space into the pharynx, flushing carbon dioxide out of the upper airways [12]. This phenomenon may help to improve the efficiency of ventilation [13] and to reduce the work of breathing [14]. HFNC oxygen is delivered through nasal cannulae, thereby reducing the dead space and making rebreathing less likely. By contrast, a reservoir mask delivering standard oxygen or a facial mask for NIV is a supplemental dead space that may promote rebreathing of carbon dioxide [15–17].

Clinical effects of HFNC oxygen therapy

Taken together, all the above-mentioned physiological effects may enable an improvement in oxygenation, a significant reduction in respiratory rate and patient effort, and better comfort with less sensation of dyspnoea (figure 1).

Improvement in oxygenation

In patients with ARF, it has been observed that P_{aO_2} is significantly increased by switching from standard oxygen to HFNC oxygen [5, 18–20]. This improvement in oxygenation could be due to a higher amount of oxygen delivered to the patient or due to the PEEP effect and subsequent recruitment. The impact of the PEEP effect on oxygenation is uncertain and its improvement seems mainly driven by higher F_{IO_2}. In a pilot study assessing standard oxygen, HFNC oxygen and NIV successively in patients with ARF, P_{aO_2} increased from standard oxygen to HFNC oxygen without changes in P_{aO_2}/F_{IO_2}, suggesting that improvement in oxygenation was directly due to an increase in F_{IO_2} [20]. By contrast, P_{aO_2} further increased with NIV with a significant increase in P_{aO_2}/F_{IO_2}, suggesting alveolar recruitment induced by PEEP. The same group then compared standard oxygen, HFNC oxygen and NIV in a large multicenter study [6]. At baseline, all patients received standard oxygen and F_{IO_2} was measured using an oxygen analyser. Again, F_{IO_2} and P_{aO_2} increased from standard oxygen to HFNC oxygen without changes in P_{aO_2}/F_{IO_2}, whereas it was markedly higher with NIV than with the other two oxygenation strategies.

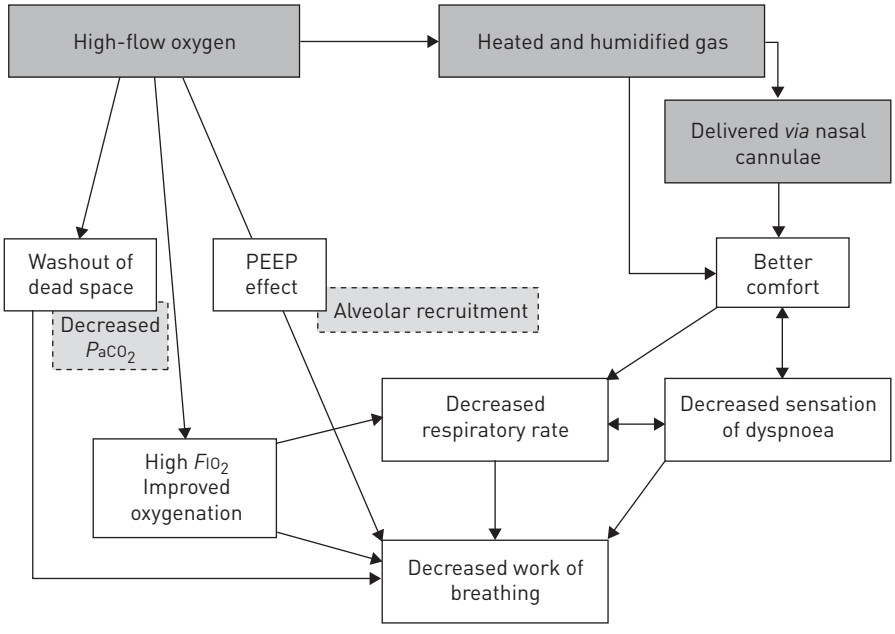

Figure 1. Impact of physiological and clinical effects on the work of breathing with high-flow nasal cannula oxygen therapy.

Decrease in respiratory rate and work of breathing

It has been found that the work of breathing in patients with ARF is lower with HFNC oxygen than with standard oxygen [14]. In this physiological study, the work of breathing was measured with a non-rebreathing mask, with HFNC oxygen or with CPAP at 5 cmH_2O [14]. The decrease in the work of breathing observed with HFNC oxygen was the same as that observed with CPAP at 5 cmH_2O. However, the mechanism by which the work of breathing decreased has not been fully elucidated. The decrease in the work of breathing could be due to decreased airway resistance, improved pulmonary compliance or only to decreased respiratory rate. Most studies have observed a rapid decrease in respiratory rate when switching from standard oxygen to HFNC oxygen in healthy subjects [21] as well as in patients with ARF and tachypnoea [5, 6, 18–20]. The respiratory rate in patients treated with HFNC oxygen was also lower than that in patients treated with NIV [6]. A recent study evaluating HFNC oxygen in post-extubation found a reduced incidence of upper airway obstruction as compared with standard oxygen [22]. Although this finding may suggest a decrease in inspiratory resistance of the upper airways, this hypothesis is unproven. The use of HFNC oxygen may also decrease the elastic work of breathing by increasing the tidal volume [21]. Tidal volumes should nonetheless remain lower than those observed with NIV. Indeed, as compared with standard oxygen or CPAP alone, the pressure support applied during NIV significantly increases tidal volumes in patients with ARF [23]. Recently, it has been suggested that the large tidal volumes generated by the pressure support may generate high transpulmonary pressures and barotrauma, worsening lung injury in patients with ARF [24, 25].

Improvement of patient comfort and breathlessness

Most studies assessing HFNC oxygen therapy have found that patients felt better comfort, less sensation of dyspnoea and less dryness of the mouth compared with standard oxygen

through a nonreservoir mask [3–5, 18]. Compared with NIV, patients treated with HFNC oxygen also had less discomfort and less breathlessness [6, 20, 26]. This improvement in comfort probably has a major impact on the clinical benefits of HFNC oxygen that we will discuss in the following section.

Clinical evidence for the use of HFNC oxygen therapy

The use of HFNC oxygen therapy to treat patients with ARF as well as to prevent hypoxaemia in various clinical settings is increasing. The results from RCTs comparing HFNC oxygen *versus* standard oxygen or NIV are detailed in table 1.

To treat acute respiratory failure

Based on observational studies, the use of HFNC oxygen in patients with ARF improved oxygenation and decreased the respiratory rate with less sensation of dyspnoea as compared with standard oxygen [5, 18, 19]. As compared with NIV, the use of HFNC oxygen was less effective in terms of oxygenation, but better tolerated with less discomfort and less breathlessness [20, 26]. The use of NIV is controversial in hypoxaemic patients and, to date, few RCTs have found a better outcome with NIV than with standard oxygen [43] and they mostly included small samples of immunocompromised patients [44, 45]. Therefore, a RCT was recently conducted by FRAT *et al.* [6] to compare these three strategies of oxygenation (*i.e.* standard oxygen, HFNC oxygen and NIV). They included 310 nonhypercapnic patients with ARF defined by a respiratory rate >25 breaths·min^{-1}, $P_{a}O_2/F_{I}O_2$ <300 mmHg and $P_{a}CO_2$ ⩽45 mmHg. The mortality rate at day 90 was lower with HFNC oxygen than using the other two strategies: 12% with HFNC oxygen *versus* 23% with standard oxygen and 28% with NIV (p=0.02). Although the rate of intubation was not significantly different among the three groups in the overall population, it was significantly lower among the more severe patients ($P_{a}O_2/F_{I}O_2$ ⩽200 mmHg) treated with HFNC oxygen than in those treated with standard oxygen or NIV (35%, 53% and 58%, respectively; p=0.009). One hour after initiation of HFNC oxygen, the dyspnoea score and discomfort felt by patients were significantly lower as compared with standard oxygen or NIV. Therefore, HFNC oxygen could be considered as the first-line strategy of oxygenation in patients admitted to the ICU for ARF. Two points from this study must be highlighted. First, patients treated with NIV received HFNC oxygen between NIV sessions and their mortality was significantly higher than in patients treated with HFNC oxygen alone. This finding suggests deleterious effects of NIV with the assumption that it might be due to high tidal volumes (mean >9 mL·kg^{-1}) and subsequent high transpulmonary pressures generated with NIV. A recent study found that nearly half of hypoxaemic patients treated with NIV had tidal volumes >10 mL·kg^{-1}, with increased risk of intubation [25]. Second, criteria for intubation were clearly defined to avoid delayed intubation that may in certain circumstances increase mortality [46]. In a retrospective observational cohort of 175 patients, late intubation beyond the first 48 h after initiation of HFNC oxygen was associated with increased mortality as compared with early intubation (67% *versus* 39%; p=0.001) [47], raising concerns about the criteria to stop HFNC oxygen for intubation. In the study by FRAT *et al.* [6], the time to intubation was not significantly different between the three groups, suggesting that poor outcomes observed in this study could be due to the oxygenation strategy applied and not to delayed intubation.

Table 1. Summary of recent (2011–2016) RCTs on high-flow nasal cannula (HFNC) oxygen therapy according to different clinical conditions

First author [ref.]	Setting	Patients n	Inclusion criteria	Main results (including primary end-points#) comparing HFNC oxygen *versus* standard oxygen or NIV
Acute respiratory failure				
FRAT [6]	ICU	310	Respiratory rate >25 breaths·min^{-1}; P_{aO_2}/F_{IO_2} ⩽300 mmHg; P_{aCO_2} <45 mmHg	*Intubation rate: 38% with HFNC oxygen* versus *47% with standard oxygen and 50% with NIV (p=0.18)* Intubation rate (P_{aO_2}/F_{IO_2} ⩽200 mmHg): 35% with HFNC oxygen *versus* 53% with standard oxygen and 58% with NIV (p=0.009) Day 90 mortality: 12% with HFNC oxygen *versus* 23% with standard oxygen and 28% with NIV (p=0.02)
LEMIALE [27]	ICU	100	Immunocompromised patients: hypoxaemia or respiratory distress	*Need for NIV or intubation at 2 h: 15% with HFNC oxygen* versus *8% with standard oxygen (p=0.36)*
FRAT [28]	ICU (subgroup analysis)	82	Immunocompromised patients: respiratory rate >25 breaths·min^{-1}; P_{aO_2}/F_{IO_2} ⩽300 mmHg; P_{aCO_2} <45 mmHg	*Intubation rate: 31% with HFNC oxygen* versus *43% with standard oxygen and 65% with NIV (p=0.04)* In-ICU mortality: 15% with HFNC oxygen *versus* 20% with standard oxygen and 42% with NIV (p=0.06) Day 90 mortality: 15% with HFNC oxygen *versus* 27% with standard oxygen and 46% with NIV (p=0.046)
JONES [29]	Emergency department	322	Hypoxia and tachypnoea	*Intubation in the emergency room: 4% with HFNC oxygen* versus *7% with standard oxygen (p=0.16)* Intubation at 24 h: 6% with HFNC oxygen *versus* 12% with standard oxygen (p=0.05)
BELL [30]	Emergency department	100	Respiratory rate ⩾25 breaths·min^{-1}; S_{pO_2} ⩽93%	*Need for escalation in ventilation therapy at 2 h: 4% with HFNC oxygen* versus *19% with standard oxygen (p=0.02)* Reduction in respiratory rate >20% at 2 h: 39% with HFNC oxygen *versus* 67% with standard oxygen (p=0.005) Reduction in Borg score at 2 h: 75% with HFNC oxygen *versus* 56% with standard oxygen (p=0.04)

Continued

Table 1. Continued

First author [ref.]	Setting	Patients n	Inclusion criteria	Main results (including primary end-points[#]) comparing HFNC oxygen *versus* standard oxygen or NIV
Hui [31]	Palliative care unit	23	Palliative cancer patients; dyspnoea score ⩾3/10 under oxygen	*Reduction in dyspnoea score at 2 h: 2/10 with HFNC oxygen* versus *3/10 with bilevel positive airway pressure (p=0.32)* Reduction in Borg score at 2 h: 2/10 with HFNC oxygen *versus* 2/10 with bilevel positive airway pressure (p=0.29)
Pre-oxygenation before intubation				
Semler [32]	ICU	150	All intubations (excluding urgent intubation)	*Lowest S_{pO_2}: 92% with HFNC oxygen* versus *90% with standard oxygen (p=0.16)* Proportion of patients with S_{pO_2} <80%: 16% with HFNC oxygen *versus* 25% with standard oxygen (p=0.22)
Simon [33]	ICU	40	Intubation in hypoxaemic respiratory failure	*Lowest mean S_{pO_2}: 89% with HFNC oxygen* versus *86% with standard oxygen (p=0.56)*
Vourc'h [34]	ICU	119	Intubation in patients with respiratory rate >30 breaths·min^{-1} and P_{aO_2}/F_{IO_2} ⩽300 mmHg	*Lowest S_{pO_2}: 92% with HFNC oxygen* versus *90% with standard oxygen (p=0.44)* Proportion of patients with S_{pO_2} <80%: 26% with HFNC oxygen *versus* 22% with standard oxygen (p=0.70)
Oxygenation during bronchoscopy				
Lucangelo [35]	Bronchoscopy room	45	S_{pO_2} ⩾90%	*P_{aO_2}/F_{IO_2} at the end of bronchoscopy: 245 mmHg with HFNC oxygen 60 L·min^{-1}* versus *165 mmHg with standard oxygen (p<0.05)*
Simon [36]	Bronchoscopy in the ICU	40	P_{aO_2}/F_{IO_2} <300 mmHg	*Lowest S_{pO_2} during endoscopy: 92% with HFNC oxygen* versus *95% with NIV (p=0.07)*

Continued

Table 1. Continued

First author [ref.]	Setting	Patients n	Inclusion criteria	Main results (including primary end-points#) comparing HFNC oxygen *versus* standard oxygen or NIV
After planned extubation in the ICU				
HERNANDEZ [22]	After planned extubation in the ICU	527	Patients intubated at least 12 h considered at low risk of extubation failure	*Re-intubation within the first 72 h: 5% with HFNC oxygen* versus *12% with standard oxygen (p=0.004)* Post-extubation respiratory failure: 8% with HFNC oxygen *versus* 14% with standard oxygen (p=0.03)
MAGGIORE [4]	After planned extubation in the ICU	105	Patients intubated at least 24 h (excluding difficult weaning and hypercapnic patients)	P_{aO_2}/F_{IO_2} *at 24 h: 287 mmHg with HFNC oxygen* versus *274 mmHg with standard oxygen (p=0.03)* Grade of discomfort at 24 h: 2/10 with HFNC oxygen *versus* 6/10 with standard oxygen (p<0.01) Re-intubation at 48 h: 4% with HFNC oxygen *versus* 21% with standard oxygen (p<0.001)
RITTAYAMAI [37]	After planned extubation in the ICU	17	Spontaneous breathing trial success	*Dyspnoea score at 30 min: 1.6/10 with HFNC oxygen* versus *2.9 with standard oxygen (p=0.04)* Respiratory rate at 30 min: 20 breaths·min^{-1} with HFNC oxygen *versus* 23 breaths·min^{-1} with standard oxygen (p=0.009)
In post-operative patients				
STÉPHAN [38]	After cardiothoracic surgery	830	Spontaneous breathing trial failure or extubation failure or high risk of post-extubation respiratory failure	*Treatment failure: 21% with HFNC oxygen* versus *22% with NIV (p=0.83)* Re-intubation: 14% with HFNC oxygen *versus* 14% with NIV (p=0.99) P_{aO_2}/F_{IO_2} at 1 h: 184 mmHg with HFNC oxygen *versus* 221 mmHg with NIV (p<0.01) Respiratory rate at 1 h: 21 breaths·min^{-1} with HFNC oxygen *versus* 23 breaths·min^{-1} with NIV (p<0.001)

Continued

Table 1. Continued

First author [ref.]	Setting	Patients n	Inclusion criteria	Main results (including primary end-points#) comparing HFNC oxygen *versus* standard oxygen or NIV
Parke [39]	After cardiac surgery	338	Cardiac surgery requiring sternotomy	S_{pO_2}/F_{IO_2} *⩾445 at day 3: 46% with HFNC oxygen* versus *42% with standard oxygen (p=0.45)* In-ICU treatment escalation: 38% with HFNC oxygen *versus* 62% with standard oxygen (p=0.001) Comfort score at day 1: 7/10 with HFNC oxygen *versus* 8/10 with standard oxygen (p<0.001)
Corley [40]	After cardiac surgery	155	Direct extubation after cardiopulmonary bypass; BMI ⩾30 kg·m^{-2}	*Atelectasis score on chest radiograph at day 1: 2 with HFNC oxygen* versus *2 with standard oxygen (p=0.70)* P_{aO_2}/F_{IO_2} at 24 h: 228 mmHg with HFNC oxygen *versus* 253 mmHg with standard oxygen (p=0.08) Respiratory rate at 24 h: 17 breaths·min^{-1} with HFNC oxygen *versus* 17 breaths·min^{-1} with standard oxygen (p=0.17) Dyspnoea score at 8 h: 1/10 with HFNC oxygen *versus* 0/10 with standard oxygen (p=0.008)
Parke [41]	After cardiac surgery	60	Respiratory rate ⩾25·min^{-1} and need for oxygen ⩾4 L·min^{-1} for 4 h or ⩾6 L·min^{-1} for 2 h	*Success at 24 h: 90% with HFNC oxygen* versus *56% with standard oxygen (p=0.006)* Need for NIV: 10% with HFNC oxygen *versus* 30% with standard oxygen (p=0.10)
Ansari [42]	After thoracic surgery	59	Post lung resection	*Better 6-min walk distance with HFNC oxygen than with standard oxygen* *Better patient satisfaction with HFNC oxygen than with standard oxygen* Length of hospital stay: 3 days with HFNC oxygen *versus* 2 days with standard oxygen (p=0.03)

#: primary end-points are given in italic.

In the subset of immunocompromised patients admitted to the ICU for ARF, two small studies have shown a reduction in intubation and mortality rate with NIV as compared with standard oxygen [44, 45]. Recently, a large RCT found no difference in terms of intubation or mortality between patients treated with NIV and those treated with oxygen alone [27]. In this last study, nearly 40% of patients received HFNC, and the mortality rate did not differ between patients treated with HFNC oxygen alone and those treated with NIV and HFNC oxygen between NIV sessions (32% with HFNC oxygen alone *versus* 25% with NIV and HFNC oxygen). Conversely, in a *post hoc* analysis including 82 immunocompromised patients, those treated with HFNC oxygen alone had a lower intubation rate than the others (31% with HFNC oxygen *versus* 43% with standard oxygen and 65% with NIV; p=0.04) [6]. Similarly, the mortality rate at day 90 was lower with HFNC oxygen than with standard oxygen or NIV (15% *versus* 27% and 46%, respectively; p=0.046). Likewise, in a retrospective cohort including 115 immunocompromised patients admitted to our ICU for ARF, patients treated with HFNC oxygen as first-line therapy had lower intubation (35% *versus* 55%; p=0.04) and mortality rates at day 28 (20% *versus* 40%; p=0.02) than those treated with NIV [48]. Thus, although its efficacy has not yet been proven, HFNC oxygen could improve the outcome of immunocompromised patients admitted to the ICU for ARF. A large-scale RCT is needed to compare HFNC oxygen with NIV in this subset of patients.

Finally, as HFNC oxygen seems well tolerated and comfortable, this strategy of oxygenation may be an alternative to NIV for end-of-life palliative care in patients suffering from ARF [31] or those with a do-not-intubate order [49].

To avoid desaturation during intubation (pre-oxygenation)

Desaturation is a common complication during intubation of hypoxaemic patients [50]. In a prospective observational cohort, S_{pO_2} <80% occurred in ~25% of patients intubated in the ICU [51]. As compared with standard oxygen, the theoretical advantage of HFNC oxygen may be first to increase P_{aO_2} and the end-expiratory lung volume before intubation, and then to maintain oxygenation during the apnoeic phase of intubation and thereby avoid desaturation [52]. In a prospective before–after study including 101 patients, the use of HFNC oxygen at a flow rate of 60 L·min^{-1} resulted in higher S_{pO_2} at the end of pre-oxygenation (median 100% *versus* 94%, respectively; p=0.007) and lower incidence of severe desaturation <80% during intubation than with standard oxygen through a non-rebreathing mask: only 2% with HFNC oxygen *versus* 14% (p=0.03) [53]. However, these encouraging results have not been confirmed in the different RCTs carried out to date [32–34]. In a recent RCT including 150 nonselected patients requiring intubation, oxygenation during the apnoeic phase did not prevent severe desaturation <80%, with a rate of 16% *versus* 25% in the group with standard pre-oxygenation without apnoeic oxygenation (p=0.22) [32]. However, oxygenation during the apnoeic phase was performed using a flow rate of only 15 L·min^{-1} [32], which is very far from that used with HFNC oxygen therapy and, thus, this study does not allow for conclusions to be drawn. In another RCT, HFNC oxygen set with a flow rate of 60 L·min^{-1} did not prevent desaturation [34]. In this study including 119 hypoxaemic patients, the lowest S_{pO_2} during intubation did not differ between the two strategies (92% with HFNC oxygen *versus* 90% with standard oxygen; p=0.44) [34]. The proportion of patients who had desaturation <80% was ~25% regardless of the strategy, a rate very close to that previously reported in the ICU [51], reinforcing the external validity of this study and suggesting an absence of benefit of HFNC oxygen for pre-oxygenation. However, a recent RCT including 40 ICU patients reported a significant drop of S_{pO_2} with standard oxygen during apnoea after the induction of

anaesthesia, whereas there was no significant decrease with HFNC oxygen [33]. Again, the lowest S_{pO_2} during intubation did not differ between the two strategies. Although HFNC oxygen therapy may have theoretical advantages for pre-oxygenation before intubation in the ICU, no significant benefit has been reported in the different RCTs conducted to date. This does not mean that HFNC oxygen is pointless for pre-oxygenation, but rather that we should wait for findings from other ongoing studies to draw sound conclusions. In a patient already treated with HFNC oxygen for ARF, it seems reasonable that pre-oxygenation should not be performed with standard oxygen and would be better carried out with HFNC oxygen or NIV.

Pre-oxygenation using NIV with F_{IO_2} 100% may be the best strategy as P_{aO_2} is markedly higher using NIV than using HFNC oxygen or standard oxygen. However, only one RCT performed in the ICU has shown a decrease in episodes of severe desaturation with NIV as compared with standard oxygen [50], while a recent retrospective trial did not find any differences between pre-oxygenation with NIV and HFNC oxygen [54]. However, the small sample size of these two studies does not allow for conclusions to be drawn and, in order to clearly identify the best strategy for pre-oxygenation in the ICU, we are currently conducting a multicenter prospective trial comparing NIV *versus* HFNC oxygen in a population of 320 hypoxaemic patients requiring intubation (ClinicalTrials.gov, trial number NCT02668458).

To avoid desaturation during invasive procedures

Fibreoptic bronchoscopy is a high-risk procedure in the ICU. In a prospective observational study including 169 hypoxaemic patients, 35% had desaturation requiring a significant increase in oxygen flow or NIV and 15% required intubation [55]. As compared with standard oxygen, the use of NIV during fibreoptic bronchoscopy could improve oxygenation and reduce the need for intubation [56]. However, HFNC oxygen therapy could be used as an alternative. A recent observational study of 30 hypoxaemic ICU patients suggested that HFNC oxygen therapy could be effective, well tolerated and safe to ensure oxygenation during nasal bronchoscopy with BAL [57].

In a RCT performed in the bronchoscopy room, 45 patients were randomised to receive standard oxygen or HFNC oxygen set at 40 or 60 $L{\cdot}min^{-1}$ [35]. Oxygenation was better in the group receiving HFNC oxygen at 60 $L{\cdot}min^{-1}$ as compared with the other two strategies (P_{aO_2}/F_{IO_2} at the end of the bronchoscopy 245 *versus* 141 mmHg with HFNC oxygen 40 $L{\cdot}min^{-1}$ and 165 mmHg with standard oxygen; $p<0.05$).

Another trial compared HFNC oxygen *versus* NIV in 40 hypoxaemic patients undergoing BAL in the ICU and found better oxygenation with NIV than with HFNC oxygen 15 min after BAL (P_{aO_2}/F_{IO_2} 220 mmHg with NIV *versus* 150 mmHg with HFNC oxygen; $p=0.002$), while the lowest S_{pO_2} during the procedure was not significantly different [36]. Again, a trial comparing HFNC oxygen *versus* NIV seems necessary to determine the best oxygenation strategy during bronchoscopy.

To prevent post-extubation respiratory distress and re-intubation in the ICU

Extubation failure occurs in ~15% of patients in the ICU and is associated with high mortality rates reaching 25–50% [58, 59]. The use of HFNC oxygen may prevent post-extubation ARF and re-intubation in this setting. In a bicentric randomised trial on 105 hypoxaemic patients extubated after at least 24 h of mechanical ventilation (P_{aO_2}/F_{IO_2} <300 mmHg after planned

extubation), oxygenation was significantly better with preventive HFNC oxygen than with standard oxygen (PaO_2/FIO_2 at 24 h 287 *versus* 247 mmHg; p=0.03) [4]. Although it was not the primary outcome, the need for re-intubation was significantly lower with HFNC oxygen than with standard oxygen (4% *versus* 21%; p=0.005). Similar results were found in a multicenter randomised trial including 527 patients considered at low risk of extubation failure [22]. In this study, the re-intubation rate at 72 h was lower in patients treated with HFNC oxygen than with standard oxygen (5% *versus* 12%; p=0.004) [22]. Most of these ICU patients were easy to wean and nearly half of them were post-operative patients with a median duration of mechanical ventilation prior to planned extubation of only 24–48 h. Although prophylactic treatment with HFNC oxygen could reduce the extubation failure rate in low-risk patients, HFNC oxygen has not yet been compared with NIV in high-risk patients, a condition where NIV could be particularly effective. In patients at high risk of extubation failure, such as elderly patients, those with underlying cardiac or respiratory disease, and especially in hypercapnic patients, the use of prophylactic NIV immediately after planned extubation remains the best strategy as it could reduce the rates of intubation [60–62] and even mortality [63, 64]. By contrast, NIV should only be used with caution to treat ARF after extubation in the ICU. Indeed, in this situation, the use of therapeutic NIV has been associated with increased mortality, probably due to delayed re-intubation [46].

To prevent respiratory distress after cardiac surgery

Post-operative hypoxia is frequent after cardiac surgery and occurs in about one-third of patients [65], and these patients may benefit from HFNC oxygen immediately after extubation. Corley *et al.* [40] randomised 155 obese patients with BMI $\geqslant 30\ kg{\cdot}m^{-2}$ to prophylactic HFNC oxygen or standard oxygen immediately after cardiac surgery. The radiological atelectasis score calculated on chest radiographs at days 1 and 5 (primary outcome) did not differ between the two groups, nor did PaO_2/FIO_2 or respiratory rate at 24 h.

In a larger trial including 338 nonselected patients who underwent cardiopulmonary bypass, the proportion of patients achieving $SpO_2/FIO_2 \geqslant 445$ mmHg (*i.e.* $SpO_2 \geqslant 93\%$ on room air) at day 3 was similar between the groups receiving HFNC oxygen and standard oxygen (46% *versus* 42%, respectively; p=0.45) [39]. However, the need for NIV or intubation based on predefined criteria was lower in the HFNC oxygen group than in the standard oxygen group (38% *versus* 62%; p=0.001), suggesting a potential benefit of HFNC oxygen in this population. The main limitation of this trial was the absence of a comparison with NIV that could reduce re-intubation, especially after thoracic surgery [66]. For this reason, Stéphan *et al.* [38] compared NIV to HFNC oxygen after cardiothoracic surgery in 830 patients at high risk of extubation failure. Treatment failure was not inferior in the HFNC group compared with the NIV group (21% *versus* 22%, respectively). However, NIV was more likely to be discontinued prematurely than HFNC oxygen (4% *versus* 1%, respectively; p=0.04), suggesting the use of HFNC oxygen as first-line therapy after cardiac surgery.

To treat acute-on-chronic lung disease?

The use of NIV is the cornerstone of first-line therapy in patients with ARF due to chronic lung disease [67, 68]. However, in patients who did not tolerate any NIV, several case reports have proposed HFNC oxygen as an alternative with better tolerance and good results (*i.e.* a decrease in $PaCO_2$ and a progressive correction of acidosis) [69, 70]. The high flow could decrease $PaCO_2$ by continuous washing of dead space and by flushing carbon

dioxide out of the airways. In a recent randomised crossover study, FRASER *et al.* [13] assessed short-term physiological responses to HFNC oxygen (30 $L \cdot min^{-1}$) in 30 COPD patients chronically treated with long-term oxygen therapy (2–4 $L \cdot min^{-1}$). They observed a rapid decrease in transcutaneous carbon dioxide, with a decreased respiratory rate and an increased tidal volume. The use of HFNC oxygen in COPD deserves to be assessed in stable patients in who inhalation of dry cold gas could be detrimental to mucociliary clearance as well as in patients with acute exacerbation between NIV sessions.

Conclusions

HFNC oxygen therapy seems to be a real technological innovation. This technique is well tolerated, easy to use and improves gas exchange without the potential deleterious effects of mechanical ventilation. Physiological effects include high FIO_2 delivery, PEEP effect and washout of dead space of the airways. Several large RCTs suggest beneficial effects in patients with ARF or in the post-extubation period. However, its use should not delay intubation if respiratory criteria for re-intubation are met or in the case of other dysfunction, especially shock or neurological failure.

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Chapter 13

Acute noninvasive ventilation

Rosanna Vaschetto[1], Federico Longhini[2] and Paolo Navalesi[2,3,4]

The use of NIV for acute respiratory failure (ARF) has progressively increased in the last two decades. In patients with ARF secondary to exacerbation of COPD, NIV largely decreases the need for intubation and invasive ventilation. Meta-analyses indicate that NIV reduces the risk of death in these patients. While strong evidence supports the use of noninvasive CPAP in patients with episodes of cardiogenic pulmonary oedema, fewer and less robust data are available on NIV for other forms of hypoxaemia, both in immunosuppressed and immunocompetent patients. NIV has been successfully applied to prevent re-intubation in post-operative patients, as a weaning strategy after early extubation and as a means to prevent post-extubation respiratory failure in at-risk patients.

The use of NIV for acute respiratory failure (ARF) has progressively increased in the last two decades. NIV provides effective ventilatory support, improving gas exchange while reducing dyspnoea and inspiratory effort, and averts the risks secondary to endotracheal intubation, both in hypercapnic and hypoxaemic patients [1]. NIV preserves airway defence mechanisms, speech and swallowing, requires less sedation, and can be easily applied and removed, as opposed to invasive ventilation [2].

In patients with ARF secondary to COPD exacerbation, NIV averts the need for intubation and invasive ventilation [3–5]. Meta-analyses [6, 7] of RCTs indicate that NIV reduces the risk of death by up to 55% [7], being the only hospital-based intervention shown able to improve mortality [7]. While strong evidence supports the use of noninvasive CPAP (n-CPAP) in addition to the standard medical treatment for acute cardiogenic pulmonary oedema (ACPO), fewer and less robust data are available on NIV for other forms of hypoxaemia, such as pneumonia and ARDS [8–11], both in immunosuppressed [9, 10, 12] and immunocompetent patients [11, 13]. NIV has been successfully applied to prevent re-intubation in post-operative patients [14, 15], as a weaning strategy after early extubation [16] and as a means to prevent post-extubation respiratory failure in at-risk patients [17–19].

Although associated with decreased rates of intubation and mortality in several patient populations, NIV requires knowledge of specific features that are crucial determinants of its outcome, such as contraindications (table 1), patient selection, location of administration, adequate monitoring and proper equipment [1].

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Table 1. Contraindications to NIV

Altered consciousness (severe agitation or encephalopathy[#])
Respiratory or cardiac arrest
Inability to protect the airways
Unmanageable secretions
Haemodynamic instability or life-threatening arrhythmia
Multiple organ failure
Upper gastrointestinal bleeding or haemoptysis
Recent facial, oesophageal, gastric or laryngeal surgery
Facial burns or trauma
Uncontrolled vomiting, bowel obstruction or gastric stasis
Patient refusal
Lack of potential recovery to acceptable quality of life
Inadequate staff to closely monitoring the patient in case of deterioration

[#]: NIV can be considered if encephalopathy secondary to hypercapnia.

Patient selection

COPD exacerbation

Exacerbations of COPD are common reasons for admission to hospital and are characterised by an elevated mortality rate (up to 30%) [3, 20]. The increased use of NIV is associated with a decreased rate of intubation and in-hospital mortality [21, 22]. NIV can be applied at different stages of severity with different objectives [23]: 1) prevention of ARF in patients who are hypercapnic but not acidotic (*i.e.* pH is normal), 2) avoidance of endotracheal intubation in established mild-to-moderate ARF and 3) as an alternative to invasive ventilation in the sickest patients without specific contraindications to NIV.

The use of NIV at a very early stage to prevent hypercapnic ARF has not proved clearly beneficial and remains debated. Two studies [24, 25] in which NIV and standard medical treatment alone were compared with mild COPD exacerbation showed no difference in any clinical outcome considered, except for a reduction in dyspnoea with NIV, although mask ventilation was found to be poorly tolerated [25]. Conversely, a large prospective multicentre RCT, also comparing NIV with standard treatment, including 342 patients with COPD exacerbation, showed that early application of NIV reduced the number of patients meeting criteria for intubation (1.4% *versus* 4.6%, p=0.002), but had no difference in terms of mortality [26]. A subgroup of patients with normal pH (n=151, pH 7.4 *versus* 7.396) showed similar benefits. However, NIV was initiated at a later stage than in other studies (24–48 h after admission) and the numbers of patients deteriorating to the point at which intubation was necessary was very high when considering the mild acidosis [26].

The strongest evidence relates to the use of NIV to avoid intubation in patients with established mild or moderate hypercapnic ARF (pH 7.20–7.35). A number of RCTs [3, 4, 5, 20, 27, 28] have shown the beneficial effects of adding NIV to the medical therapy in this patient population, producing an improvement in dyspnoea [5, 20], vital signs and gas exchange [3, 5, 20], and a reduction of endotracheal intubations [3–5], infectious (both respiratory and nonrespiratory) complications [29, 30], length of hospital stay [3, 27] and mortality [3, 5].

Although infrequent, because of the rapid onset of ARF, its progression and/or delays in receiving medical evaluation and appropriate treatment, patients may worsen to a point at which mechanical ventilation becomes mandatory. If the patient does not meet other contraindications to NIV, this technique may still play a role in these more severe patients by eliminating the additional resistive load [31] and the increased risk of superimposed pulmonary infections [32] determined by the endotracheal tube. Two RCTs compared NIV with invasive ventilation in patients with these characteristics [33, 34]. In both studies, the mean pH was ~7.2. In the study by CONTI *et al.* [33], the rate of survival was similar; however, in patients with successful NIV treatment, the lengths of ICU and hospital stay were shorter, and there were less complications and fewer hospital readmissions in the following year. The study by JURJEVIC *et al.* [34] found that NIV was associated with a shorter duration of ventilation and ICU stay, less ventilator-associated pneumonia, and a reduced number of tracheotomies; the rate of mortality, however, was similar in the two groups. These studies suggest that applying NIV at a later stage is less likely beneficial, but some patients may still benefit. In severely acidotic patients, SQUADRONE *et al.* [35] showed that a NIV attempt before proceeding to intubation and invasive ventilation did not harm the patients and NIV may be attempted with caution, closely monitoring the patients in an ICU and avoiding excessive delay in intubation.

As shown in figure 1, NIV can be profitably used at all stages of severity of hypercapnic ARF due to COPD exacerbation. In addition, NIV also plays a role in facilitating weaning and extubation of COPD patients requiring intubation. Following the seminal work of NAVA *et al.* [36], several studies have subsequently confirmed the potential of NIV for this purpose [37]. Furthermore, as COPD patients who are extubated after a successful

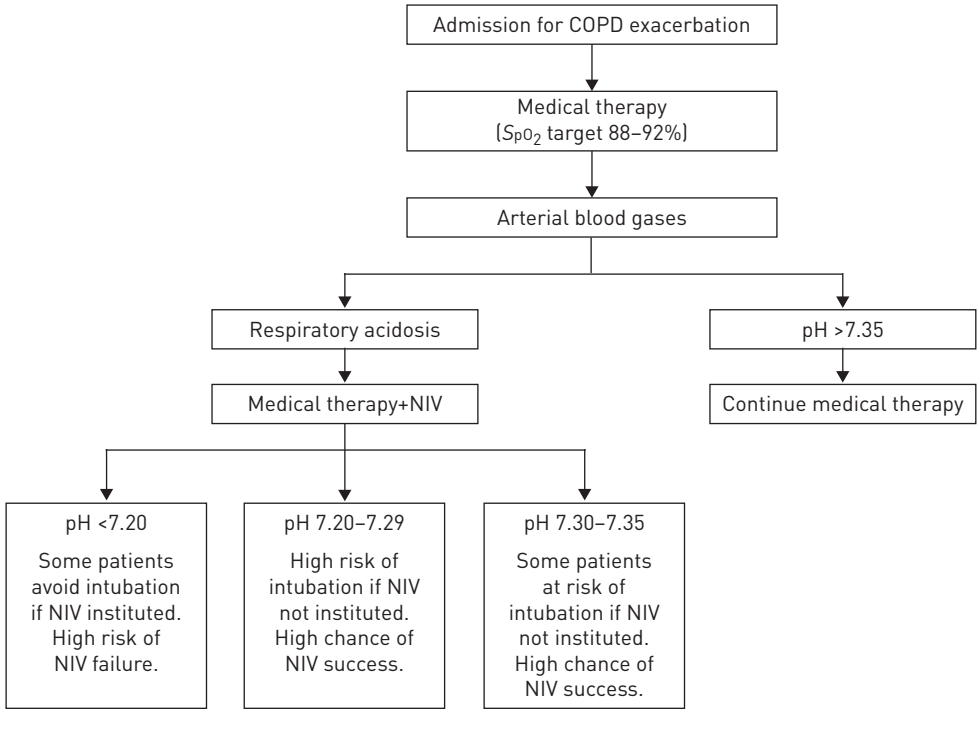
Admission for COPD exacerbation
Medical therapy
($Sp0_2$ target 88–92%)
Arterial blood gases
Respiratory acidosis
pH >7.35
Medical therapy+NIV
Continue medical therapy
pH <7.20
Some patients avoid intubation if NIV instituted. High risk of NIV failure.
pH 7.20–7.29
High risk of intubation if NIV not instituted. High chance of NIV success.
pH 7.30–7.35
Some patients at risk of intubation if NIV not instituted. High chance of NIV success.

Figure 1. Flow chart for treatment of COPD exacerbations.

spontaneous breathing trial have an increased risk of post-extubation respiratory failure, the preventive application of NIV soon after extubation has proven effective in reducing the rate of re-intubation [17–19]. The overall role of NIV in the management of hypercapnic ARF in patients with COPD is summarised in figure 2.

Episodes of acute-on-chronic respiratory failure sustained by causes other than COPD can also be successfully treated by NIV [38]. Consequent to the increasing prevalence of extreme obesity, obesity hypoventilation syndrome (OHS) has become a common cause of hypercapnic ARF. In acute OHS, NIV appears to be as effective as in COPD [39].

Cardiogenic pulmonary oedema

Exacerbation of congestive heart failure leading to ACPO is the single most frequent cause of hospitalisation for individuals aged ⩾65 years and the in-hospital mortality rate can be as high as 12% [40]. Strong evidence supports the use of n-CPAP in addition to the standard medical treatment for ACPO. A Cochrane systematic review and meta-analysis, including 32 studies and 2916 participants, found that n-CPAP or bilevel positive airway pressure (*i.e.* NIV) significantly reduced the need for endotracheal intubation (relative risk 0.52, 95% CI 0.36–0.75) and hospital mortality (relative risk 0.66, 95% CI 0.48–0.89) [41]. Nevertheless, when n-CPAP and bilevel positive airway pressure were compared individually with standard therapy, only n-CPAP demonstrated a statistical improvement in mortality [41]. According to the data, one death is avoided for every nine ACPO patients treated with n-CPAP. It should be noted that this meta-analysis excludes any additional risk of acute myocardial infarction with NIV, compared with standard medical care (relative risk 1.24, 95% CI 0.79–1.95), a concern following the findings of earlier studies [42–44]. Inexpensive and easy to implement, n-CPAP is widely recognised as the first-line intervention in this patient population [45], while bilevel positive airway pressure does not seem to add benefit, even in the more severe hypercapnic patients.

De novo (hypoxaemic) ARF

Whether or not patients with hypoxaemic ARF due to reasons other than ACPO may also benefit from NIV is questionable. Different from COPD, these patients often need near-continuous support, which is commonly required for a longer time than in ACPO. In hypoxaemic patients, NIV failure was found to be associated with increased mortality irrespective of ARF severity [46], which was attributed to erroneous patient selection, higher risk of emergency intubation and additional lung injury caused by the increased transpulmonary pressure [46–48]. Intermittent applications of NIV delivered with low PEEP levels have been shown to be of no benefit and even detrimental in patients with pneumonia [12, 48], but to be beneficial in post-operative patients [14, 15, 49]. In these patients, n-CPAP without inspiratory support is also beneficial, as opposed to standard oxygen therapy [49, 50]. Hypoxaemic patients with immunosuppression are, in principle, those more likely to benefit from NIV, while those with ARDS are the least likely to benefit [51].

Immunocompromised patients

The survival of immunocompromised patients has improved in recent years, likely due to advances in diagnostic and therapeutic options [52]. Unfortunately, the number of immunocompromised patients with severe complications requiring treatment in the ICU has

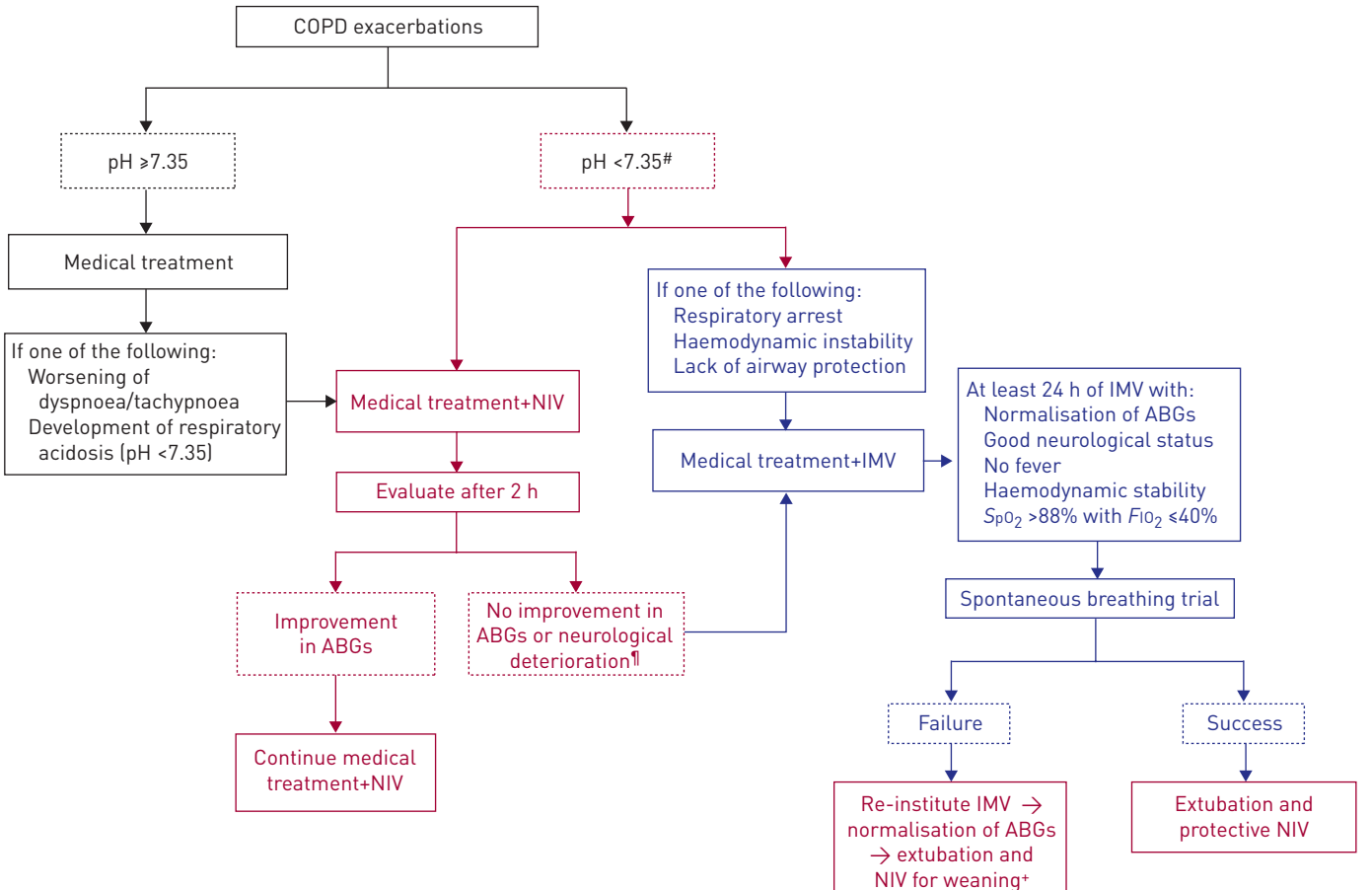

Figure 2. Flow chart depicting the overall approach to hypercapnic acute respiratory failure. ABG: arterial blood gas; IMV: invasive mechanical ventilation. #: see figure 1 for more details; ¶: unless NIV ceiling of treatment; +: expertise required.

also increased [53]. ICU admission is necessary in up to 15% of patients with acute leukaemia [54] and 20% of bone marrow transplantation recipients [55], and the main reason for ICU referral is ARF. Although mechanical ventilation is the main supportive therapy for those with severe gas exchange impairment, the need for intubation has been consistently indicated as one of the most adverse factors in these patients [56–58]. Early use of NIV was shown to positively affect patient outcome in a few small single-centre RCTs. In a cohort of solid organ transplant patients with ARF, ANTONELLI *et al.* [9] demonstrated decreased rates of intubation (20% *versus* 70%, p=0.002) and mortality (20% *versus* 50%, p=0.05) in patients randomised to NIV, as opposed to those receiving only standard therapy. HILBERT *et al.* [10] compared intermittent NIV with the sole medical therapy in 52 patients with immunosuppression of different causes, presenting with pulmonary infiltrates, fever and hypoxaemic ARF, as defined by the presence of dyspnoea at rest, respiratory rate >30 breaths·min^{-1} and a $P_{a}O_2/F_{I}O_2$ ratio <200 mmHg while breathing oxygen. The patients who received NIV in addition to the medical treatment had fewer intubations and lower mortality. Data from a multicentre database, which prospectively included 1302 patients with haematological malignancies admitted for ARF to 158 Italian ICUs between 2002 and 2006, demonstrated similar mortality rates between the patients initially treated with NIV and those undergoing invasive ventilation *ab initio* [59]. One single-centre RCT investigated the potential role of early n-CPAP in patients with haematological malignancies [60]. The authors found that the delivery of n-CPAP in the medical ward reduced the occurrence of ICU admission for mechanical ventilation [60]. Based on these data, NIV has been considered in many centres as the first-line approach for ARF in patients with various causes of immunosuppression [47].

More recently, however, the benefit of NIV for immunocompromised patients has been questioned [12, 61, 62]. LEMIALE *et al.* [12] performed the largest randomised clinical trial to date, with the aim of assessing whether NIV could improve patient outcome. For this purpose, 374 immunocompromised patients with $P_{a}O_2$ <60 mmHg in room air, respiratory rate >30 breaths·min^{-1} and/or signs of respiratory distress were randomised to receive NIV or conventional oxygen therapy. No difference was found between the two groups in terms of day-28 mortality and rate of intubation, ICU-acquired infections, duration of mechanical ventilation and length of ICU stay. However, these results may have been affected by some methodological limitations potentially reducing the ability to detect the possible benefit of NIV [62, 63], such as a lower than expected mortality rate, making the study likely underpowered, and the significantly higher proportion of patients receiving high-flow nasal oxygen in the control group. In addition, NIV was applied with low levels of PEEP and for relatively short periods.

Further studies are necessary to clarify the potential of NIV in immunocompromised patients, which may be affected by several factors, such as underlying disease, ARF severity, timing and modalities of NIV application.

ARDS

The Berlin Definition of ARDS proposes a possible role for NIV in the milder forms of ARDS, *i.e.* $P_{a}O_2/F_{I}O_2$ ⩽300 and >200 mmHg with PEEP ⩾5 cmH_2O [64]. The use of NIV in patients with ARDS is, nonetheless, controversial and studies evaluating the role of NIV in the ventilator treatment of ARDS are scarce. In a prospective cohort study, ANTONELLI *et al.* [65] applied NIV in 147 ARDS patients admitted to the ICU who were not yet intubated. NIV improved gas exchange and avoided intubation in 54% of patients. Avoidance of intubation was associated with lower rates of ventilator-associated pneumonia (2% *versus* 20%) and ICU mortality (6% *versus* 53%).

Two RCTs evaluated NIV in nonhypercapnic immunocompetent patients with *de novo* hypoxaemic ARF. DELCLAUX *et al.* [11] reported no beneficial effects and a higher number of adverse events in patients receiving n-CPAP. FERRER *et al.* [13] randomised 105 subjects with severe hypoxaemic ARF to receive either NIV or oxygen therapy with high F_{IO_2}. The respiratory failure aetiologies were predominantly pneumonia and cardiogenic pulmonary oedema, but there were also 15 individuals with ARDS. NIV prevented intubation, reduced the incidence of septic shock and improved survival in a very select population of patients; however, ARDS was associated with the highest risk of NIV failure [13]. A meta-analysis [66] focusing on these two RCTs [11, 13] and another study conducted in solid organ transplant recipients [9] concluded that the addition of NIV to standard care in patients with ARDS did not reduce either intubation rate or ICU mortality. RANA *et al.* [67] assessed the outcome of subjects with ARDS initially treated with NIV. All those with shock failed NIV. Metabolic acidosis (odds ratio 1.27, 95% CI 1.03–0.07 per unit of base deficit) and severe hypoxaemia (odds ratio 1.03, 95% CI 1.01–1.05 per unit decrease in P_{aO_2}/F_{IO_2}) predicted NIV failure.

Very recent data by PATEL *et al.* [68], however, open a new perspective on the use of NIV in ARDS by means of a helmet. 83 ARDS patients undergoing NIV through a face mask for at least 8 h were randomly assigned to continue NIV by the face mask or switch to a helmet for NIV support. The study was interrupted early for efficacy. The intubation rate was 61.5% with the mask and 18.2% with the helmet ($p<0.001$), with increased ventilator-free days in the helmet group (28 *versus* 12.5 days, $p<0.001$). The mortality rates at 90 days were 34.1% in the helmet group and 56.4% in the face mask group. Although the results of this single-centre study are interesting and promising, external validation is needed [68].

In patients with ARDS due to H1N1 influenza virus infection, KUMAR *et al.* [69] found that 33% of subjects initially received NIV, with a failure rate as high as 85%. The reported rate of NIV failure averaged 52% (from 14% to 70%) [70]. The rate of failure was, however, lower in mild ARDS (34%) than in moderate or severe ARDS (68%) [71]. Crucial predisposing factors for NIV failure included altered level of consciousness and shock [71]. NICOLINI *et al.* [72] found the early application of NIV to avoid invasive ventilation in H1N1 patients to be associated with an overall success rate of 48%. Patients presenting at admission with a high SAPS (Simplified Acute Physiological Score) II score and a low P_{aO_2}/F_{IO_2} and/or unable to promptly correct gas exchange were at higher risk of intubation and death.

A recent international observational study found 15% of all patients with ARDS received NIV in routine care [73]. Nonetheless, the studies available at present suggest extreme caution in the use of NIV in ARDS [46, 74, 75].

Technical aspects

Some logistical and technical aspects assume crucial importance for NIV outcome. Location, ventilators, interfaces and use of sedatives are the most important, and deserve particular attention.

Location

The location of NIV treatment is an important predictor of the outcome of NIV in patients with ARF [75]. NIV is used in different settings, such as the emergency room, ICU, respiratory ICU, step-down unit and general ward. Successful use of NIV has been shown

in post-operative care units [14, 76]. Data from a recent North American study [77] showed that NIV is most frequently initiated in ICUs and emergency departments, but the rate of utilisation is also high in the general wards where a fifth of NIV is initiated. This study also showed that the actual location depends on ARF aetiology: in patients with acute-on-chronic lung disease and ACPO, NIV is started more often in emergency departments, while for "*de novo*" hypoxaemic ARF it is started more often in the ICU. Patients with hypercapnic ARF who respond promptly to NIV can also be effectively treated in the medical ward [78, 79], while those with a poor response should be treated wherever intubation can be promptly performed. In the pre-hospital setting, interesting results in terms of reduction of mortality and intubation rates have been obtained by early application of NIV, especially in the form of n-CPAP in patients with ACPO [80].

The decision on where to deliver NIV should be made considering the type of ARF, severity of illness, need for monitoring, ICU bed availability, and capabilities of the location to provide monitoring, staff skills and experience [70–72].

Ventilators

The ventilator is crucial in determining NIV success in the acute setting [81]. Dedicated NIV platforms perform better than ICU ventilators using the NIV algorithm. In particular, advances in software technology offer newer algorithms that enhance interactions (and synchrony) between the patient and ventilator [81].

The ability to tolerate air leaks is important for the functioning of ventilators for NIV. Leaks are either intentional leaks through the passive exhalation port or unintentional leaks, frequently as a result of loose-fitting interfaces. Originally designed for home care purposes, bilevel ventilators always compensate for leaks; more recently, enhanced monitoring and graphics capabilities have allowed improved tuning of ventilator settings [75]. Whereas in the past ICU ventilators were not designed to work in the presence of leaks, the vast majority of these devices nowadays incorporate NIV-dedicated modules intended for detecting, monitoring and compensating for air leaks. Some features, such as trigger type and sensitivity, adjustable flow cycling-off threshold and maximal inspiratory time, allow adjustments aimed at improving patient–ventilator interactions and synchrony [81, 82].

The performance of NIV ventilators has been predominantly evaluated on the bench, often with varying criteria [83]. In a laboratory and clinical study by Carteaux *et al.* [81], bilevel ventilators outperformed critical care ventilators for NIV use with respect to patient–ventilator interaction and synchrony. New modes of mechanical ventilation, such as neurally adjusted ventilatory assist (NAVA) [84, 85], have been shown to significantly add to interaction and synchrony, but the clinical importance of these improvements remains to be determined.

Interfaces

The interface is an important determinant for NIV success, which holds particularly true for prolonged NIV applications [23]. The availability and quality of NIV interfaces has substantially increased over the past decade [2]. Navalesi *et al.* [86] evaluated nasal prongs, and oronasal and nasal masks for NIV application in 26 stable hypercapnic patients with either COPD or restrictive thoracic disorders who had not received NIV. They found all three interfaces effective in improving gas exchange; the nasal mask being better tolerated

than the two other interfaces, but less effective in decreasing $PaCO_2$ [86]. As acute patients with ARF are generally mouth breathers, nasal interfaces are infrequently used in acute patients. In patients receiving NIV for COPD exacerbation, however, ANTON *et al.* [87] found no differences between nasal and facial masks in terms of patient effort, gas exchange and inspiratory effort. A subsequent study comparing oronasal and nasal masks in ARF patients found the two interfaces to have similar effects regarding improvement in vital signs and gas exchange, and rate of NIV failure and intubation, but the nasal mask was less well tolerated in terms of comfort [88]. In patients with hypercapnic ARF, GIRAULT *et al.* [89] assessed the influence of the mask used for initiating NIV (facial *versus* nasal) on efficacy and tolerance. They found mask failures occurred significantly more often with the nasal mask primarily due to air leaks and concluded that the facial mask should be used in the initial management of hypercapnic ARF [89].

In a study evaluating four interfaces for NIV in ICU patients, FRATICELLI *et al.* [90] found that despite differences in internal volume, *i.e.* very high (977 mL), high (163 mL), moderate (84 mL) or virtually no internal volume, there were no major effects due to the internal dead space on minute ventilation, work of breathing and gas exchange. NIV was successful in reducing the patient's inspiratory effort regardless of the interface. The only important difference observed related to air leaks and asynchronies that were greater with the mouthpiece, *i.e.* the interface with the smallest dead space, which also resulted in reduced comfort [90]. These data indicate that NIV interfaces are largely interchangeable, supporting a "rotating" strategy for reducing the risk of skin breakdown and intolerance [2].

Two new interfaces have been made available for clinical use more recently: the total full face mask, incorporating the eyes within the perimeter of the mask in addition to the nose and mouth, and the helmet, containing the whole head inside a transparent hood that, in its standard configuration, is joined by a rigid plastic ring to a soft collar and secured by two padded armpit braces at four hooks.

With the total full face mask the seal is around the perimeter of the face, thereby avoiding contact on the nasal bridge, *i.e.* the area most commonly affected by bruises consequent to skin friction [91]. OZSANCAK *et al.* [92] found the oronasal and total full face mask were equally tolerated by patients with a similar time of application, while CHACUR *et al.* [93] reported improved comfort with the total full face mask, which allowed longer NIV application but did not improve NIV outcome. LEMYZE *et al.* [94] evaluated the effects of changing the mask, from an oronasal mask to a total full face, in 74 do-not-intubate patients after NIV failure to reverse ARF. After switching the mask, NIV reversed ARF and led to hospital survival in 64% of the patients who had previously failed NIV.

The helmet has been shown to improve NIV comfort over time compared with the oronasal mask, eliminating facial skin breakdown, gastric distension and eye irritation [91, 92]. Despite these advantages, the helmet has specific drawbacks primarily related to its highly compliant soft collar [95]. Inspiratory pressure dissipation increases the time lag between inspiratory effort and ventilator assistance, worsening patient–ventilator synchrony and resulting in less efficient reduction of the patient's inspiratory effort [81, 94, 95]. In addition, the armpit braces that maintain the helmet in place may cause patient discomfort and axillary skin lesions leading to NIV intolerance and failure [96]. To overcome these limitations, a new helmet has been recently developed and introduced in clinical use, in which an opening ring placed underneath an inflatable cushion secures the helmet without the need for armpit braces and reduces the pressure dissipated because of the downward

displacement of the soft collar during ventilator insufflation. Studies on the bench [83], in healthy volunteers [97] and in ICU patients [98] indicate this new helmet is effective in improving patient–ventilator interaction, as opposed to the standard version. A pilot multicentre RCT found this new helmet equally effective as the face mask in delivering NIV to patients with hypercapnic ARF [99].

Sedation

Despite the aforementioned strategies, some patients remain intolerant, in particular following application for long periods and/or with elevated airway pressure, causing NIV discontinuation and the subsequent requirement for endotracheal intubation. The administration of analgesia and sedation in an attempt to reverse this situation is controversial [100, 101]. While the "preventive" administration of sedation and analgesia, *i.e.* at initiation of NIV, has so far not shown encouraging results [102], the "curative" infusion of opioids [103, 104], propofol [105] or dexdemethomidine [106] was seen to be beneficial in small uncontrolled studies for the treatment of discomfort and NIV intolerance, being able to avoid intubation in a large fraction of intolerant patients [105, 106]. Whereas it is important to note the different respiratory effects of these drugs [107–109], recent data suggest that combining sedative and analgesic drugs during NIV worsens NIV outcome, while the separate administration of single drugs does not [102]. Finally, it is worth remarking that sedative infusion should not be considered for managing patients outside the ICU.

Conclusions

NIV is nowadays a valid tool for treating patients with ARF. NIV should be used for early treatment of established episodes of hypercapnic ARF, in order to avoid further deterioration and intubation, and to prevent post-extubation respiratory failure and re-intubation in patients at increased risk of extubation failure because of predisposing conditions such as the presence of underlying respiratory and cardiac diseases. Evidence also supports the use of n-CPAP in addition to the standard medical treatment for patients with ACPO. A skilled team may also advantageously use NIV to facilitate weaning and extubation. Uncertainty remains about the possible role of NIV in the treatment of patients who are hypoxaemic because of pneumonia or ARDS, in which NIV is not advisable at present. It should be noted that, unless NIV is the ceiling of treatment, one should always be ready to intubate patients who do not improve with NIV. Some specific technical aspects are crucial and deserve careful attention to increase the chance of applying NIV to the right patient in the appropriate setting with the appropriate equipment, and thus improve the overall rate of success.

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Chapter 14

Extracorporeal carbon dioxide removal

Christian Karagiannidis[1], Stefan Kluge[2], Stephan Strassmann[1] and Wolfram Windisch[1]

Extracorporeal carbon dioxide removal ($ECCO_2R$) is an emerging technology in ICU medicine aimed at compensating for severe respiratory acidosis. Thereby, $ECCO_2R$ aims at immediately saving lives or reducing complications related to intubation and subsequent invasive mechanical ventilation by either avoiding intubation or allowing protective ventilation or early extubation following initial intubation. $ECCO_2R$ can be applied by pumpless arteriovenous (av-$ECCO_2R$) and pump-driven venovenous (vv-$ECCO_2R$) systems. Both systems require the cannulation of large vessels and are associated with technique-specific complications, most importantly bleeding, ischaemia and clotting. Therefore, the potential benefits of $ECCO_2R$ must be balanced against the possible complications in each individual. However, scientific evidence for $ECCO_2R$ is limited, and restricted to only a few experimental and clinical trials. Despite this, $ECCO_2R$ has been suggested to be live saving in selected patients when adequately considering the potential complications. Furthermore, technical developments have allowed $ECCO_2R$ to become widespread and larger RCTs are now in progress. Thus, $ECCO_2R$ is suggested to become an established treatment option in the near future in ICU medicine.

Extracorporeal carbon dioxide removal ($ECCO_2R$) is a rapidly developing live-saving technique in ICU medicine aimed at treating very severe respiratory acidosis, avoiding intubation and subsequent long-term invasive mechanical ventilation or shortening the time spent on invasive mechanical ventilation by allowing early extubation in patients with acute hypercapnic respiratory failure following ventilatory insufficiency, most importantly COPD [1–4]. In addition, $ECCO_2R$ is also capable of compensating for respiratory acidosis occurring in patients with severe ARDS and lung protective ventilation [5–7].

This chapter will summarise our knowledge on $ECCO_2R$ in the context of the emergency situation. The chapter starts with a description of the technical considerations of $ECCO_2R$. Next, possible complications but also the suggested benefits of $ECCO_2R$ are

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discussed. This is followed by a summary of the current literature on the clinical applications of $ECCO_2R$. Finally, future directions and unmet needs are addressed.

Technical considerations of $ECCO_2R$

In principle, $ECCO_2R$ can be applied in two different ways: pumpless arteriovenous (av-$ECCO_2R$) (figure 1) and pump-driven venovenous (vv-$ECCO_2R$) (figure 2). The pumpless arteriovenous system, also known as interventional lung assist (iLA; Novalung, Heilbronn, Germany), utilises the natural pressure gradient between the arterial and venous systems, *i.e.* femoral artery and vein (figure 1). Av-$ECCO_2R$ provides a substantial shunt between the arterial and venous sides, and thus sufficient cardiac output is mandatory for this approach. Accordingly, blood flow rates range between 1.0 and 2.0 $L{\cdot}min^{-1}$ depending on cannula size and cardiac output [8]. As the oxygenator of the system has a low resistance with a pressure drop of <10 mmHg under optimal circumstances, blood flow is mainly dependent on the diameter and resistance of the draining arterial cannula. On average, a 15-French draining cannula with a slightly larger venous backflow cannula generates a blood flow of ~1.6 $L{\cdot}min^{-1}$ and a 17-French cannula generates a blood flow of 2.0 $L{\cdot}min^{-1}$ [8]. Depending on blood flow, sweep gas flow (see below) and baseline $PaCO_2$, av-$ECCO_2R$ systems are capable of removing ~50% of the total carbon dioxide production of patients on mechanical ventilation, *i.e.* ~150 $mL{\cdot}min^{-1}$ of carbon dioxide. In contrast, oxygenation capability is low and reaches ~40 $mL{\cdot}min^{-1}$ of oxygen, which is ~10% of the estimated oxygen consumption. One major problem with av-$ECCO_2R$ is that arterial cannulation can lead to poor perfusion of the relevant limb and leg with subsequent ischaemia depending on the anatomical circumstances of the artery. In addition, there are only limited regulatory possibilities for av-$ECCO_2R$. Therefore, this approach is restricted in clinical application, particularly in emergencies, and thus its use has decreased during recent years when considering the alternative approach of vv-$ECCO_2R$ systems [9].

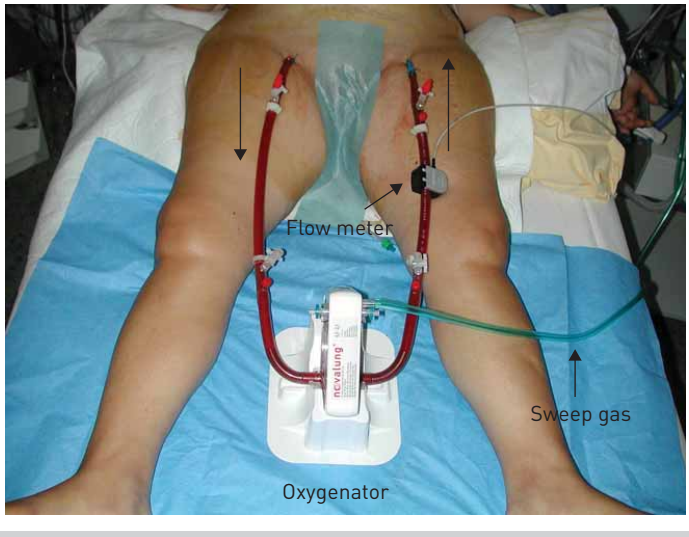

Figure 1. Arteriovenous extracorporeal carbon dioxide removal system. Cannulation of the right femoral artery and left femoral vein with pumpless gas exchange through a low-resistance oxygenator. Photograph kindly provided by Alois Philip (University of Regensburg, Regensburg, Germany).

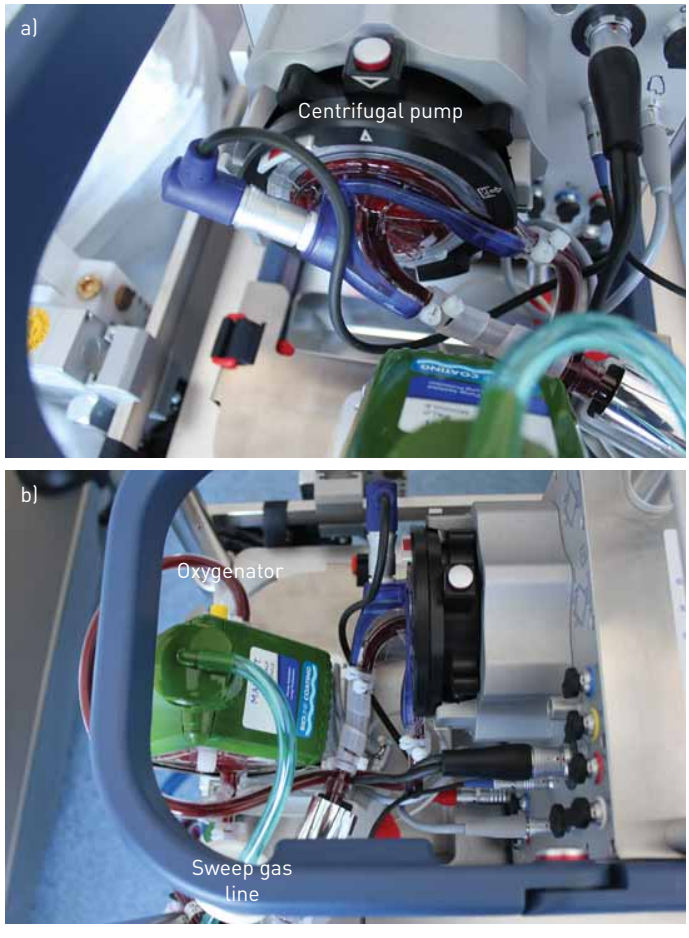

Figure 2. a) Venovenous extracorporeal carbon dioxide removal system driven by a centrifugal pump through an electromagnetic field. b) Oxygenator with a surface area of 0.98 m^2 with green sweep gas line. For primary carbon dioxide removal, 21% or 100% oxygen can be used as sweep gas.

Further advances in $ECCO_2R$ systems have been achieved with the developments in vv-ECMO systems [9] over the last 5–10 years. Basically, heparin-coated vv-$ECCO_2R$ systems consist of two venous cannulae (one draining and one backflow) or one double-lumen cannula, a polymethylpentene membrane lung and a blood pump (figure 2). Importantly, no clear recommendations on how to choose blood flow rates for vv-$ECCO_2R$ have been established. Thus, blood flow rates range between 200 $mL \cdot min^{-1}$ and 2 $L \cdot min^{-1}$ according to different trials [1, 3], but are still lower than rates chosen for full vv-ECMO used to treat severe hypoxaemia in ARDS patients [10]. Very low blood flow rates are similar to the flow rates used for haemodialysis [11], whereas higher flow rates of up to 2 $L \cdot min^{-1}$ are derived from high-flow vv-ECMO systems. Correspondingly, some $ECCO_2R$ systems are driven by roller pumps comparable to haemodialysis systems, whereas others are driven by centrifugal pumps comparable to high-flow ECMO systems (table 1). Accordingly, when considering the different systems available for vv-$ECCO_2R$ the crucial question is how much blood flow is required for sufficient carbon dioxide removal, especially in the emergency situation. Here, one should consider that the amount of carbon dioxide removal achieved by vv-$ECCO_2R$ depends on four key factors: 1) blood flow, 2) sweep gas flow, 3) surface area of the oxygenator and 4) venous carbon dioxide tension (P_{vCO_2}) [12, 13].

Table 1. Currently available extracorporeal carbon dioxide removal systems

Device	Manufacturer	Blood flow	Oxygenator surface area	Pump
CARDIOHELP 5.0	Maquet, Rastatt, Germany	Maximum 5 $L \cdot min^{-1}$	1.2 m^2	Centrifugal pump
iLA activve	Novalung, Heilbronn, Germany	0.25–4.5 $L \cdot min^{-1}$ depending on oxygenator	0.32–1.3 m^2	Centrifugal pump
Hemolung	Alung, Pittsburgh, PA, USA	350–550 $mL \cdot min^{-1}$	0.59 m^2	Centrifugal pump
PrismaLung/PRISMAFLEX	Baxter, Unterschleißheim, Germany	Maximum 450 $mL \cdot min^{-1}$	0.32 m^2	Roller pump
ApherCap	Aferetica, Mirandola, Italy	30–450 $mL \cdot min^{-1}$	Not published	Roller pump
Abylcap	Bellco, Mirandola, Italy	Maximum 450 $mL \cdot min^{-1}$	0.67 m^2	Roller pump
DECAP	Hemodec, Salerno, Italy	<500 $mL \cdot min^{-1}$	0.3–1.35 m^2	Roller pump
Interventional lung assist (iLA)	Novalung, Heilbronn, Germany	Depending on cardiac output and cannula size, usually <2.0 $L \cdot min^{-1}$	1.3 m^2	Pumpless, arteriovenous

Again, the blood flow rate is suggested to be one of the most important determinants of the amount of carbon dioxide removal. Interestingly, recent experimental research has determined that even low blood flow rates of 200–400 mL·min^{-1} with a conventional haemodialysis catheter are capable of removing significant amounts of carbon dioxide, but are not sufficient to counterbalance severe respiratory acidosis. Although up to 80 mL·min^{-1} can be removed with a blood flow of 400 mL·min^{-1}, the corresponding pH does not increase to the normal range if a severe respiratory acidosis exists. For this purpose, blood flow rates >750–1000 mL·min^{-1} have been shown to be required for normalising severely acidotic pH values, *i.e.* removing up to 150 mL·min^{-1} of carbon dioxide, corresponding to 50–60% of the estimated carbon dioxide production [13].

However, even though low blood flow rates have less effects on real carbon dioxide removal, clinical data in acidotic COPD patients indeed suggest significant improvements in pH and reduction in P_{aCO_2} even with the application of low blood flow rates of ~250 mL·min^{-1}, and this may be attributed to an improved breathing pattern in dynamically hyperinflated patients [4]. In addition, increasing sweep gas flow rates help to augment carbon dioxide removal, but this effect is limited [13].

Low-flow vv-ECCO$_2$R systems require smaller draining and backflow cannulae in the range of 13–19 French or a small double-lumen cannula (16.5–20 French). Therefore, implantation is less risky and can be performed in the emergency situation even in awake patients under local anaesthesia [14]. As an alternative, modern double-lumen cannulae can be implanted in the jugular vein (figure 3) guided by ultrasound or even fluoroscopy, or, as an alternative, into the femoral vein. Although the concept of a double-lumen cannula seems to be attractive, only 150 out of nearly 2000 vv-ECMO patients treated in 2014 in Germany had double-lumen cannulation [9]. However, especially with regard to cannula size and positioning, implantation even in the emergency situation is less risky than in high-flow ECMO.

As already noted, the primary physiological aim of ECCO$_2$R is the improvement in blood gases. However, another physiological consequence of ECCO$_2$R with subsequent reduction of P_{vCO_2} is the decrease of pulmonary artery pressures, which are typically high in patients with acute respiratory acidosis that is linked to hypercapnia, and this is true for patients with both COPD [15] and ARDS [16].

Complications of ECCO$_2$R

Complications of extracorporeal systems may be significant and must be balanced against the established benefits. The main technical complication relates to the activation of the coagulation system and, therefore, clotting and bleeding [3, 10, 17]. Unfortunately, low-flow systems are more prone to clot than high-flow systems and, thus, require more aggressive anticoagulation. Although there is currently insufficient data, an activated prothrombin time of 1.5–2.0 times the normal range may be recommended to avoiding excessive clotting. As patients on extracorporeal systems are more prone to heparin-induced thrombocytopenia type II, up to 10% of all patients develop this complication [18]. Furthermore, case–control studies and case series [3, 4, 19] report major and minor bleeding complications, which can limit treatment success and may even lower the benefits of ECCO$_2$R. In this regard, it must be acknowledged that cannulation, especially in the emergency situation, also represents a substantial risk for perforation with concomitant major bleeding. Nevertheless, life-threatening

Figure 3. a) Extracorporeal carbon dioxide removal ($ECCO_2R$) in acute exacerbation of COPD with a jugular double-lumen cannula. Initial high-intensity NIV with early NIV failure was not successful on day 1. b) Note that lid oedemas due to high P_{ACO_2} before $ECCO_2R$ disappeared 1 day later.

complications are less often observed compared with high-flow ECMO and occur only in a small percentage of all patients. However, at present $ECCO_2R$ should be restricted to experienced centres with the possibility to adequately respond to major complications, such as bleeding following vessel perforation or coagulation activation.

Potential applications and pathophysiological considerations of $ECCO_2R$ in acute hypercapnic respiratory failure

Noninvasive and invasive mechanical ventilation are well-established treatment options for acute hypercapnic respiratory failure. However, despite optimal treatment some patients remain severely hypercapnic, resulting in respiratory acidosis with pH values <7.20, and this is particularly true for severe airway obstruction as in COPD or asthma. Potentially, these patients might be candidates for $ECCO_2R$ as long as the long-term prognosis is suggested to be favourable. Life-threatening cases of asthma may be treated by $ECCO_2R$ as long as no severe hypoxaemia occurs, since reversibility of airway obstruction is typical of

the disease. One potential application relates to the management of huge bronchopleural fistulae, which may hinder carbon dioxide removal and are usually aggravated by mechanical ventilation [20]. Fuehner *et al.* [14] demonstrated that ECMO in awake patients, also including primary $ECCO_2R$, serves as a better bridge to transplant than invasive mechanical ventilation. Although this group of patients is small, $ECCO_2R$ is also an increasingly recognised emergency option for patients bridged to transplant as long as oxygenation is possible without extracorporeal systems.

Another potential application of $ECCO_2R$ is in severe COPD patients with early or late NIV failure. It is well accepted that invasive mechanical ventilation is associated with several complications, most importantly infectious complication [21], that worsen the prognosis of patients with an acute exacerbation [22]. Therefore, it has been suggested that avoidance of mechanical ventilation by $ECCO_2R$ may improve outcomes. Interestingly, in acute exacerbation of COPD, $ECCO_2R$ has more impact on the pathophysiology of the disease than only reducing $PaCO_2$. We could show that carbon dioxide removal leads to a lowering of initially high pulmonary arterial pressure in acute exacerbation, since carbon dioxide is a well-know vasoconstrictor of the pulmonary vessels [15]. Furthermore, lowered carbon dioxide leads to a reduction of the respiratory drive and therefore breathing frequency, which in turn further reduces dynamic hyperinflation and therefore carbon dioxide [19]. The effect on lowering HCO_3^- with $ECCO_2R$ during several days of treatment to prevent re-exacerbation is under current investigation and may also be a secondary beneficial effect.

Finally, uncompensated respiratory acidosis following protective or ultraprotective mechanical ventilation in ARDS is a promising field for $ECCO_2R$ [6, 7], which will be further evaluated in the future.

Current clinical data

The current clinical evidence is very limited. Nevertheless, there is no doubt that life-threatening severe respiratory acidosis resistant to established treatment strategies can be successfully addressed by $ECCO_2R$. Therefore, $ECCO_2R$ has the potential to be life saving. Recently, two case–control studies [4, 19] and a number of case series [2, 23] have been published. Del Sorbo *et al.* [4] showed avoidance of intubation for patients at risk of NIV failure following vv-$ECCO_2R$ establishment. Four major and nine minor complications were reported in 25 patients, mainly major and minor bleeding and circuit clotting. In a retrospective study, Kluge *et al.* [19] demonstrated that intubation could be avoided in 19 out of 21 patients treated with av-$ECCO_2R$. Further case series led to the impression that avoidance of invasive mechanical ventilation is possible and technically feasible, but associated with significant side-effects. In a recent review, Sklar *et al.* [3] summarised the evidence in $ECCO_2R$ in 87 patients with severe COPD. $ECCO_2R$ was shown to be capable of preventing intubation in 65 out of 70 patients (success rate 93%) and allowing extubation in nine out of 17 patients (success rate 53%). However, time of extubation, cannulation in the emergency setting, weak coughing after extubation requiring frequent bronchoscopy and bleeding complications have been suggested to be major limiting factors.

In a very recent study by Braune *et al.* [24] these limitations led to an intubation rate of 44% in patients with COPD failing NIV for acute hypercapnic respiratory failure despite $ECCO_2R$ being started successfully. In addition, a third of all cases had relevant side-effects.

Conclusion and future directions

$ECCO_2R$ has the potential to avoid complications related to invasive mechanical ventilation, can be live saving and is, therefore, suggested to become an established treatment option in the near future in ICU medicine. However, the current scientific evidence for $ECCO_2R$ is sparse and complications related to $ECCO_2R$, most importantly bleeding and clotting, may counterbalance its benefits. Therefore, there is a need for further RCTs in acute airway obstruction, most importantly exacerbation of COPD, in the emergency situation, when respiratory acidosis cannot be sufficiently equalised by conventional treatment strategies including NIV. Planned and ongoing trials (ClinicalTrials.gov, trial number NCT02086084; further trials upcoming) are needed to address the following important issues: the impact of the underlying disease, indication criteria, technical differences of the various approaches and impact of complications on outcome. Furthermore, $ECCO_2R$ should not be regarded as a standalone treatment option, but rather should be viewed in the context of preceding and subsequent treatment modalities, and this is suggested to be particularly true for patients with end-stage disease, such as with COPD.

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Chapter 15

Acute bronchoscopy

Raffaele Scala

Acute bronchoscopy has a pivotal role in the bronchoscopy unit and intensive care settings. In the bronchoscopy unit, flexible bronchoscopy (FBO) is helpful for the diagnosis of intrathoracic tumours, interstitial lung diseases and suspected pneumonia, while rigid bronchoscopy with/without FBO is useful to manage central airway obstruction, haemoptysis and removal of inhaled foreign bodies. In intensive care settings, FBO is used to facilitate intubation in difficult airways scenarios, guide percutaneous dilatational tracheostomy and resolve lobar/lung atelectasis. "Bronchoscopic" sampling should be considered in suspected ventilator-associated pneumonia only if "noninvasive" techniques are inconclusive, as well as in nonventilated immunosuppressed patients. Despite the variable quality of evidence that exists in favour of the combined use of NIV and bronchoscopy in different scenarios, the best evidence supports prophylactic NIV to prevent intubation in nonventilated patients. The role of high-flow nasal cannula oxygen in "assisting" FBO needs to be further investigated. Benefits of acute bronchoscopy should be weighed against the risk of cardiopulmonary complications, bleeding and pneumothorax.

Bronchoscopy represents a fundamental technique for the management of patients admitted to respiratory high-dependency care units (RHDCUs) and ICUs [1, 2]. It is not a coincidence that the first application of bronchoscopy in 1897 was for the emergency removal of an inhaled foreign body [3, 4].

Bronchoscopy can be performed with flexible and rigid instruments. Flexible bronchoscopy (FBO) is widely used thanks to its lower invasiveness, the ability to explore larger regions of the bronchial tree and its shorter learning curve; its "ancillary techniques" allow sampling from the lung and mediastinum, such as BAL, protected specimen brushing (PSB), transbronchial needle aspiration (TBNA) and transbronchial lung biopsy (TBLB) [1, 2, 4]. By transmitting images from the tip of the instrument to a video camera instead of an eyepiece, video bronchoscopy is of help in performing FBO procedures that can be better followed by all the team members. Although rigid bronchoscopy has a narrower range of applications, it maintains a crucial role when performing interventional procedures, such as ablative therapies (*e.g.* laser, argon plasma coagulation, electrocautery and cryotherapy), airway stenting, as well as in removing foreign bodies [3, 4].

This chapter will focus on the acute clinical indications for bronchoscopy in adults both in the bronchoscopy unit and the ICU/RHDCU, the pathophysiological pitfalls of bronchoscopy

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in nonventilated and ventilated patients, as well as the role of NIV and/or high-flow nasal cannula (HFNC) oxygen in "assisting" high-risk patients during bronchoscopy.

Clinical indications for acute bronchoscopy

The main indications for acute bronchoscopy and listed in table 1 and include: 1) to help/guide procedures for airway management (*e.g.* difficult intubation and percutaneous dilatational tracheostomy (PDT)) [5–7], 2) to support the diagnosis of infective and noninfective lung infiltrates in nonventilated and ventilated patients [1, 8–12], 3) to manage airway obstruction of various aetiology (*e.g.* such as mucous plugs, foreign bodies and benign/malignant tracheobronchial diseases) [3, 4, 13], and 4) to manage massive haemoptysis [14].

Acute bronchoscopy in the bronchoscopy unit

Pneumonia

Even if FBO is not routinely recommended in nonventilated patients with suspected or known severe community-acquired (CAP) or hospital-acquired pneumonia (HAP) because its risks may outweigh the benefit of determining the responsible pathogen(s), early BAL and/or PSB should be strongly considered in immunosuppressed patients and/or in patients potentially infected with multidrug-resistant microorganisms [1, 8, 9].

Acute interstitial lung diseases

The two most common scenarios of acute interstitial lung diseases (ILDs) are: 1) rapid deterioration of a previously diagnosed ILD and 2) initial presentation with rapidly progressive ILD [10]. In the former scenario, the differential diagnosis should consider either a progression of the known underlying ILD, or a superimposed infection or other

Table 1. Indications for acute bronchoscopy

Bronchoscopy unit	Intensive care settings
Diagnostic tool	**Diagnostic tool**
Acute intrathoracic tumours	Ventilator-associated pneumonia
Severe community/hospital-acquired pneumonia	Severe community/hospital-acquired pneumonia[#]
Acute interstitial lung diseases	Acute interstitial lung diseases[#]
Therapeutic tool in airway obstruction	Intrathoracic tumours[#]
Atelectasis due to mucous plug	**Therapeutic tool in airway obstruction**
Benign or malignant central airway obstruction	Atelectasis due to mucous plug[#]
Inhaled foreign body	**Supportive tool for interventional procedures**
Management of massive haemoptysis	Endotracheal intubation in difficult airways
	Percutaneous dilatational tracheostomy
	Positioning of double-lumen endotracheal tube
	Risky extubation

[#]: in mechanically ventilated patients by means of noninvasive or invasive ventilation support.

noninfective causes. In the latter scenario, the acute presentation may represent the exacerbation of a previously unrecognised ILD (*e.g.* idiopathic pulmonary fibrosis (IPF)) or a "*de novo*" condition such as acute interstitial pneumonia, fulminant organising pneumonia, acute eosinophilic pneumonia, or, less frequently, diffuse alveolar damage in occult connective tissue disease, vasculitis or hypersensitivity pneumonia. However, the differential diagnosis in "*de novo*" presentation should always consider processes other than primary ILD (*e.g.* infection, cardiogenic pulmonary oedema, alveolar haemorrhage syndromes or drug-induced pneumopathy). Considering the diagnostic flow chart in acute ILDs, high-resolution CT should be always done before performing bronchoscopy to increase the diagnostic yield of BAL and TBLB [10].

BAL plays a crucial role in the diagnosis of infective ILD, especially in immunosuppressed patients [1, 15], and may be helpful for excluding infection in "acceleration" of IPF or other ILDs [10, 16–18]. In the case of progression of known progressive fibrotic ILD, FBO procedures are not appropriate and palliative approach is warranted [18].

The added value of TBLB in patients with acute respiratory failure (ARF) undergoing BAL is controversial, especially in the case of known idiopathic ILDs [1, 10, 19–23]. Conversely, in severely immunosuppressed patients with pulmonary infiltrates, granulomatous diseases (*e.g.* sarcoidosis) and lymphangitis carcinomatosis, TBLB may be more diagnostically sensitive than BAL [19, 21].

Transbronchial lung cryobiopsy (TBLC) has been recently proposed as a less invasive alternative to surgical lung biopsy (SLB) in ILD [24]. TBLC yields larger and better-preserved specimens as compared with TBLB, but smaller specimens than SLB. Diagnostic yields, mortality and complication rates for TBLC fall somewhere between those observed for TBLB and those observed for SLB [25, 26]. Despite its potential benefits, there are no data regarding the use of TBLC in ARF [24–26]. In hypoxaemic patients, TBLC may be safely performed under HFNC oxygen or NIV in units where its life-threatening complications can be quickly treated.

Intrathoracic tumours

Challenges in performing acute FBO for the diagnosis and staging of intrathoracic tumours are correlated with the presence of chronic respiratory failure, central airway obstruction (CAO), severe bleeding, superior vena cava syndrome and extrapulmonary metastases [1, 13, 14, 27].

Severely hypoxaemic patients with/without hypercapnia may safely undergo diagnostic bronchoscopy under the assistance of NIV or HFNC oxygen [28, 29]. Management of CAO due to malignant infiltration and/or extrinsic compression (*e.g.* bulky adenopathies) and treatment of severe haemoptysis are reported later in this chapter. The impaired systemic venous return due to superior vena cava syndrome may facilitate FBO-correlated haemorrhagic complications [27]. Furthermore, coexisting chronic cardiopulmonary diseases and the use of anticoagulant and/or antiplatelet therapy increase the likelihood of periprocedural hypoxaemia and bleeding, respectively [1]. The risk of neurological complications (*e.g.* epilepsy and intracranial hypertension) during acute FBO is greater in patients with cerebral metastases for whom a prophylactic treatment should be considered. In the case of liver and/or renal failure, doses of sedatives and local lidocaine should be carefully adjusted [1, 27].

Haemoptysis

Massive haemoptysis causing ARF and/or haemodynamic instability is a life-threatening emergency with a mortality ranging from 7% to 80% [14]. The usefulness of bronchoscopy for the management of haemoptysis (*e.g.* identification of sources of bleeding and endobronchial treatments) varies depending on the clinical scenario [30, 31].

CT and bronchoscopy should be performed in every case of haemoptysis, if the origin and cause of the bleeding are not already known. In peripheral bleeding, diagnostic bronchoscopy is necessary to identify the origin in order to guide either radiological intervention with bronchial arterial coils or surgical resection. In life-threatening acute bleeding, waiting for the CT scan is not recommended and the patient should be transferred directly to the bronchoscopy unit [31]. The priority in patients with ongoing massive haemoptysis is the immediate protection of the airways by means of endotracheal intubation with either an endotracheal tube (ETT) or rigid bronchoscopy [3, 4, 32]. Performing FBO through an ETT or rigid bronchoscopy may be helpful for suctioning and exploring the bronchial tree as well as for implementing acute strategies to stop the bleeding. The bleeding can be efficiently controlled by means of rigid (with or without flexible) bronchoscopy in the case of peripheral bleeding (*e.g.* blocker balloon, tamponade or spigot) or central bleeding (*e.g.* argon plasma coagulation or laser ablation) [31]. Interventional bronchoscopic procedures are effective to manage massive bleeding of endoscopically visible bronchogenic carcinoma [3, 4, 14].

Despite bronchoscopic instillation of adrenaline and other substances [33–35] and endobronchial tamponade with balloon catheters [36] having been attempted to stop bleeding, the efficacy of these empirical therapies is unproven [1, 14, 31]. Furthermore, FBO may facilitate selective intubation of the unaffected lung with a single- or double-lumen ETT [32, 37], thus buying time to address the bleeding in the affected lung. In nonmassive haemoptysis, FBO is usually performed within 24–48 h in stable patients [38]. Localisation of the site of bleeding can be achieved in a larger proportion of cases by combining FBO with CT [39, 40]. FBO may also be useful when haemoptysis occurs in invasively ventilated patients (*e.g.* diffuse alveolar haemorrhage).

Atelectasis

Despite the widespread clinical use of FBO in the bronchoscopy unit to treat atelectasis in nonventilated patients, there are no published studies in favour of this practice [41]. This does not mean that FBO is not indicated to remove mucous plugs, but simply that the effectiveness of this procedure remains unproven [1]. In this scenario, FBO may be useful to exclude the coexistence of benign or malignant endobronchial stenosis.

Central airway obstruction

In the case of malignant or benign CAO, patients should undergo interventional bronchoscopy as early as possible in experienced hands before invasive mechanical ventilation (IMV) becomes necessary. Interventional procedures lead to quick symptom relief and are beneficial to enable further etiological therapy [13]. In patients with CAO of different aetiologies necessitating IMV and admission to the ICU/RHDCU, preliminary data suggest that rigid bronchoscopy procedures (*i.e.* ablative therapies and/or airway stenting) are a

feasible, safe and successful means of weaning from ventilation, providing potential benefits in terms of prolonging survival, reducing hospital stay, allowing additional cancer treatments and palliating symptoms [42–44].

Inhaled foreign bodies

In contrast to children, tracheobronchial foreign body aspiration is uncommon in adults [45]. However, life-threatening ARF could be a dramatic presentation of foreign bodies in adults, especially in those with dysphagia, neurological disorders, and alcohol and sedative abuse [46]. The tracheobronchial tree should be quickly examined with FBO in all suspected cases. The oral route should be used as foreign bodies may not pass through the nasal cavity when retrieved from the tracheobronchial tree. FBO extraction should be attempted by a trained physician in a setting where rigid bronchoscopy is readily feasible in the case of CAO, failure, complications (*e.g.* haemorrhage and displacement) or need for ventilatory support [46]. Physicians should be careful not to push foreign bodies more distally during FBO extraction as it may become impossible to remove them endoscopically, making thoracotomy necessary. Displacement of the foreign body or a fragment of it into the contralateral lung or trachea with subsequent complete CAO is a potentially lethal complication. Rigid bronchoscopy allows better control of the airway and easier manipulation of foreign bodies with different types of forceps or cryotherapy probes [45]. This is why foreign body extraction should be primarily performed using rigid bronchoscopy whenever possible. Performing FBO through rigid bronchoscopy allows identification of distal foreign bodies. FBO is preferable to rigid bronchoscopy in mechanically ventilated patients or in the case of spine/craniofacial fractures that prevent the manipulations required for rigid bronchoscopy [45]. The success rate of FBO extraction in adults ranges from 60% to 90% [45–47].

Acute bronchoscopy in intensive care settings

Ventilator-associated pneumonia

Except for some scenarios (*e.g.* severe sepsis, multiorgan dysfunction and shock) for which antibiotic therapy should not be delayed while awaiting microbiological results, all patients with suspected ventilator-associated pneumonia (VAP) should undergo lower respiratory tract sampling before any introduction/change of antibiotics [11, 12, 48]. In suspected VAP, bronchoscopic or "invasive" (*e.g.* BAL and/or PSB) and nonbronchoscopic or "noninvasive" techniques (*e.g.* tracheobronchial aspiration or mini-BAL) are used to obtain respiratory samples [12, 49, 50]. Both "invasive" and noninvasive" samples can be analysed either "quantitatively" with a threshold count of bacterial growth to differentiate between infection and colonisation (*e.g.* PSB: 10^3 CFU·mL^{-1}; BAL: 10^4 CFU·mL^{-1}; endotracheal aspirates: 10^5 CFU·mL^{-1}) or "qualitatively" (presence or absence of pathogenic germs) [51, 52]. Uncontrolled studies [53–58] showed great heterogeneity (*e.g.* gold standard for diagnosis, microbiological thresholds and employed techniques), a wide range of sensitivities of bronchoscopic techniques (51–100%) and variable comparison with "noninvasive" techniques [1]. A recent systematic review [12], including five RCTs [55, 59–62] for a total of 1367 immunocompetent patients with VAP, did not show any significant differences in mortality rates, influence on antibiotic change, days of IMV and length of ICU stay between either "quantitative" *versus* "qualitative" analysis or "invasive" *versus* "noninvasive" sampling techniques. According to the evidence, FBO should be considered only if

"noninvasive" techniques fail to identify a responsible organism. The available data do not address the issue of diagnosis of "non-VAP" in ventilated patients (*e.g.* severe CAP that requires subsequent ventilation) [1, 12] (figure 1).

Acute interstitial lung diseases

The choice of admitting acute ILD patients in the ICU/RHDCU and performing FBO procedures is strongly dependent on the likelihood of a successful outcome, based on reasonable clinical judgement and a high-resolution CT pattern showing that the underlying ILD ("non-IPF" diseases) and/or the superimposed trigger (*e.g.* opportunistic infection) are likely to be reversible [10]. Evidence of extensive fibrotic alterations or of an "IPF pattern" without superimposed acute disease usually indicates that FBO procedures and IMV are highly unlikely to be successful [18].

Similar to its use in the bronchoscopy unit, BAL plays a crucial role in the ICU for the diagnosis of infection in either previously known ILDs or in "*de novo*" ILDs, especially in high-risk conditions (*e.g.* neutropenia, immunosuppressive therapy and haematological malignancies) [10]. Moreover, BAL may be helpful in excluding infection and supporting the diagnosis of "acceleration" of a known IPF [10, 18]. BAL may also be safely performed under NIV in severely hypoxaemic ILD patients [28, 63]. BAL findings may be useful in the delicate decision-making process dealing with withholding or withdrawing ventilation. The added value of TBLB to BAL in ILD patients admitted to the ICU/RHDCU should be carefully weighed against its potential risks [10, 18]. In nonintubated patients, the rate of TBLB complications (*e.g.* pneumothorax and haemorrhage) may be acceptable (<5%) assuming that SLB could be avoided. Conversely, pneumothorax following TBLB in IMV patients may lead to life-threatening deterioration in gas exchange [22]. In a series of 13 invasively ventilated patients with progressive infiltrates [20], TBLB established the diagnosis in six cases, but significant complications occurred in four cases (n=2 pneumothorax requiring drainage, n=1 pulmonary haemorrhage and n=1 arrhythmia). On the basis of this limited evidence, TBLB should be used cautiously in highly selected IMV patients. In a pilot study [63], TBLB allowed a definite diagnosis in five out six severely hypoxaemic ILD patients (n=2 malignancy, n=1 lymphoma, n=1 sarcoidosis and n=1 *Pneumocystis* pneumonia) requiring NIV, with one subject intubated for haemoptysis.

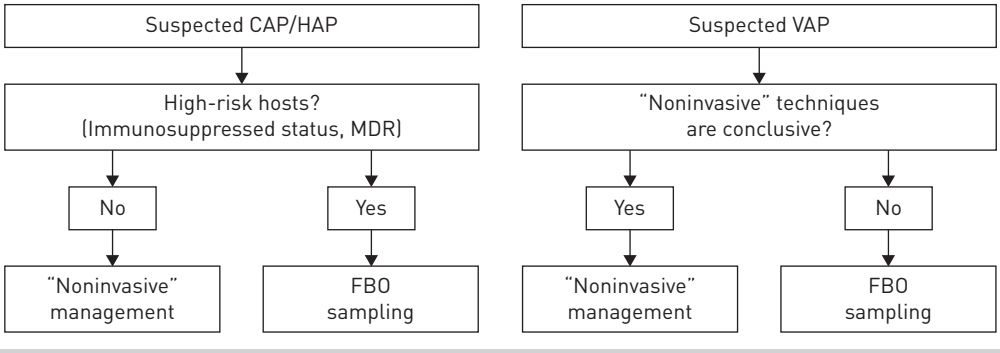

Figure 1. Role of bronchoscopic techniques in the diagnosis of pneumonia in nonventilated and ventilated patients. CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; MDR: multidrug resistance; FBO: flexible bronchoscopy.

Intrathoracic tumours

The risk of performing FBO in IMV patients with suspected lung cancer is correlated with the patient's condition, reduced calibre of the ETT and complications of bronchoscopic sampling [1]. Concerning the latter, while TBLB may be associated with catastrophic complications in IMV patients, this is not the case for TBNA. In a retrospective study of eight invasively ventilated patients with abnormal lymph nodes [64], TBNA showed a sensitivity of 83% and a specificity of 100%; in five cases (63%), TBNA led to a change in management without complications. Even though there are no available data in ARF, endobronchial ultrasound-guided TBNA could be easily performed in ventilated patients and is of higher diagnostic value than "blind" TBNA [65].

Atelectasis

Although FBO is widely used to treat atelectasis due to mucous plugs in intubated patients, the evidence for its usefulness is scant [1, 41]. Small case series [66–68] reported variable success rates (19–89%) of FBO in IMV patients, showing a better response for lobar than for subsegmental atelectasis. Some earlier studies suggested, but did not prove, that BAL or high-pressure insufflations though a balloon-tipped catheter may be of additional benefit to reverse atelectasis [1, 41]. Two small RCTs [69, 70] performed in intubated patients demonstrated a similar efficacy of FBO *versus* aggressive chest physiotherapy either for prevention of post-lobectomy atelectasis or as treatment for atelectasis after physiotherapy failure [71, 72]. Accordingly, FBO may be considered only in selected intubated patients who develop lobar atelectasis that does not resolve with physiotherapy [1, 41].

Difficult intubation

Intubation with FBO (*i.e.* fibreoptic intubation (FOI)) is considered a mainstay of anticipated and unanticipated elective difficult airways management in awake, spontaneously breathing patients [5, 71–73]. The advantages of FOI over the other techniques are particularly evident in patients with cervical spine injury, such as maintenance of the head and neck in a neutral position, reduction of the risk of aspiration, identification of a coexistent airway trauma, and avoidance of complications due to incorrect ETT placement [74, 75]. In comparative studies, no differences was seen in terms of the rate of successful intubation between FOI and other techniques, such as a laryngeal mask airway (LMA) and video laryngoscopy; conversely, FOI was associated with longer intubation times and a higher incidence of hypoxaemia [76–78]. In clinical scenarios in which nonemergency intubation is deemed necessary and mask or supraglottic ventilation (*e.g.* a LMA) is unlikely to be successful or poses an aspiration risk, awake FOI is recommended because the drawbacks of general anaesthesia are avoided (*e.g.* inadequate ventilation and loss of upper airway patency) [5]. Pitfalls of FOI in an emergency should be carefully considered (table 2). The success and safety of FOI presuppose adequate time for preparation, a cooperative spontaneously breathing patient, as well as experience in handling FBO. Consequently, this technique is not indicated in an anticipated "cannot intubate/cannot ventilate" situation. In acute patients who require immediate intubation (*e.g.* severe respiratory distress, impending respiratory arrest, cardiovascular instability and burden of airway secretions), it is crucial to assess the feasibility of either bag manual ventilation or NIV to safely support patients during FOI. In the case of an unanticipated

Table 2. Indications of intubation under the guidance of flexible bronchoscopy and pitfalls in the emergency setting

Indications
Known or suspected difficult laryngoscopy (*e.g.* macroglossia, limited mouth opening, receding lower jaw, short thyromental distance, protruding teeth, Mallampati class III/IV and obesity)
Known or suspected cervical spine instability
Anatomic abnormalities (*e.g.* congenital airway deformities, head and neck malformations, and cancers)
Head, neck, spine and upper airway trauma
Pitfalls
Time-consuming procedure requiring expertise in handling the bronchoscope
Not a feasible procedure in "cannot intubate/cannot ventilate" scenarios
Need for adequate oxygenation and ventilation (*i.e.* manual bag ventilation, noninvasive ventilation and ventilation *via* supraglottic devices) during the procedure
High risk of failure in the case of deep analgo-sedation due to reduced airway visibility (*i.e.* tongue obstruction)

"cannot intubate/cannot ventilate" condition, FOI should be attempted only when ventilation may be guaranteed with supraglottic devices [5, 77, 78].

FOI can be performed in awake patients with topical anaesthesia alone using the "spray-as-you-go" technique [5, 79]. Analgo-sedation may be considered judiciously [5, 80–82]. If "conscious sedation" with preserved spontaneous breathing increases the patient's cooperation and facilitates FOI, a deeper sedation may cause fall back of the tongue with reduced airway visibility and severe hypoxaemia. Concerning the route of access, the nasal approach is anatomically favourable in that the laryngeal opening is more easily seen with the fibrescope [5], particularly in patients with a large tongue, limited mouth opening, receding lower jaw or tracheal deviation. If nasal introduction is difficult, the oral route should be chosen to prevent bleeding. If performed orally, FOI may be facilitated by either manual manoeuvres (*e.g.* jaw thrust and tongue protrusion), or various oral bite blocks, intubating airway and supraglottic devices or a laryngoscope blade [5, 77]. Additionally, specialised face masks allow oxygen administration, and manual masks and NIV maintain ventilation during FOI attempts. For both nasal and oral access, a video laryngoscope or rigid/semirigid bronchoscope can be used in combination with FBO to perform the intubation under direct vision, thereby avoiding airway trauma [5]. Adequate size matching between the ETT and the external diameter of the bronchoscope (gap $\leqslant$1.5 mm) permits less play between them and may avoid the ETT becoming caught at the level of the epiglottis or the arytenoid cartilages [5]. Any resistance to advancement should be overcome by rotating the ETT 90° counterclockwise. Potential complications of FOI include epistaxis, laryngotracheal trauma, laryngospasm, gastric distention and aspiration [5].

Tracheostomy and other applications

PDT has almost completely replaced surgical tracheostomy in the ICU/RHDCU because of its advantages, such as bedside feasibility and fewer complications (*e.g.* haemorrhage, pneumothorax, emphysema, tracheomalacia and stenosis). Compared with the "blinded" manoeuvre, "FBO-guided" PDT reduces the rate of pneumothorax, uncorrected placement of cannulae and tracheal back wall damage [6, 7]. Furthermore, FBO prevents accidental extubation, allows removal of secretions and treats endobronchial haemorrhage [6, 7, 83].

However, there are some pitfalls of "FBO-guided" PDT: 1) hypercarbia with increased intracranial pressure in neurological patients, 2) risk of bleeding or malplacement in patients with difficult anatomy, coagulopathy, obesity or previous tracheostomy and 3) high repair costs due to accidental needle puncture of the bronchoscope [84]. Real-time ultrasound guidance is a safer alternative to FBO in these high-risk conditions [6, 83, 84].

Among other applications, FBO is helpful for positioning double-lumen ETTs, endobronchial blockers, tubes and stents in patients with CAO and massive haemoptysis. FBO is also useful in risky extubation, specifically to assess pharyngeal airway swelling, vocal cord function and subglottic stenosis [85].

Pitfalls and remedies of bronchoscopy in nonventilated and ventilated patients

Bronchoscopy in nonventilated patients

FBO induces important cardiopulmonary effects in nonintubated patients (figure 2) [1, 2, 4, 86–88]. By occupying 10–20% of the normal tracheal lumen, FBO increases airway resistance and causes "air trapping" (*i.e.* intrinsic PEEP), both of which may reduce gas exchange and augment work of breathing. FBO-induced hypoxaemia becomes worse when BAL is performed and suction is applied, due to ventilation–perfusion mismatch and end-expiration

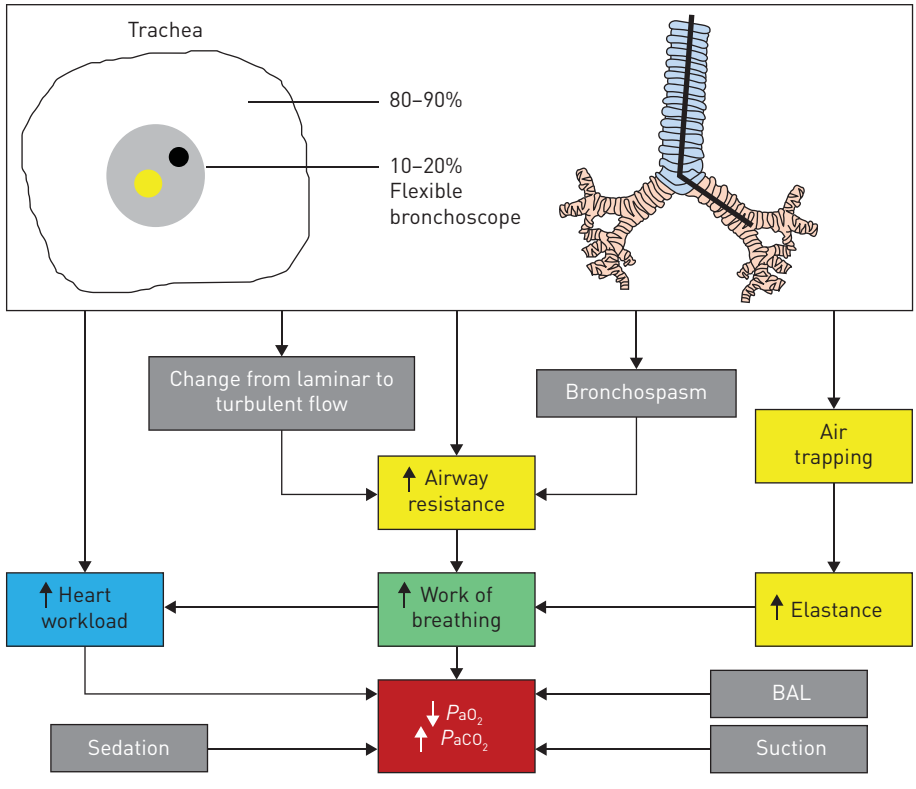

Figure 2. Pathophysiology of cardiopulmonary changes during bronchoscopy.

alveolar closure, respectively. FBO causes P_{aO_2} to decrease by 10–20 mmHg [1, 2, 4, 86–88]. Additionally, analgo-sedation during FBO may induce hypoventilation [89]. These pulmonary changes persist after the procedure and the time that the gas exchange takes to normalise ranges from 15 min in normal subjects to >24 h in patients with cardiopulmonary diseases [90]. Furthermore, bleeding and pneumothorax complicating biopsy procedures may precipitate life-threatening ARF [1, 2, 87]. FBO-induced sympathetic stimulation and hypoxaemia could increase cardiac output. Decreased intrathoracic pressure caused by the augmented respiratory muscle effort produces an increase in right ventricular preload and left ventricular afterload. Consequently, FBO may trigger cardiac arrhythmias, and, less frequently, cardiogenic pulmonary oedema and acute coronary syndrome [91]. These cardiopulmonary changes are more exaggerated during rigid bronchoscopy procedures because of the greater size of the instrument, prolonged suctioning, low F_{IO_2} (to prevent combustion hazard during laser resection) and deeper analgo-sedation [92].

Despite these relevant cardiopulmonary effects, the findings of the studies evaluating the risks of FBO in hypoxaemic nonventilated patients are contrasting [87, 88]. It was reported that BAL performed in the ICU did not significantly increase intubation requirements in critically ill cancer patients, as compared with "noninvasive" diagnostic tests [93]. In a prospective study performed in 169 nonintubated hypoxaemic patients undergoing FBO, a third of the procedures were complicated by increased ventilatory support: NIV for "oxygen-supported" patients and IMV for "noninvasively supported" patients. Intubation was required in 15% of cases, but it occurred 2 h after FBO in 4% of cases [94]. Nevertheless, FBO is not recommended if hypoxaemia cannot be corrected to at least P_{aO_2} 75 mmHg or to S_{pO_2} >90% with supplemental oxygen [1, 95]. When FBO is mandatory, IMV can ensure adequate ventilation during the manoeuvre, but exposes patients to the risk of severe complications (*e.g.* baro/volutrauma, VAP and prolonged weaning) [1, 28, 87].

Bronchoscopy during NIV

There is a strong pathophysiological rationale for combining FBO and NIV in critically ill patients because the limitations of one technique may be counterbalanced by the properties of the other [28, 87]. NIV prevents FBO-induced cardiopulmonary alterations by means of unloading respiratory muscles, and improving gas exchange and heart performance. Moreover, keeping the patient on NIV after FBO may prevent the risk of post-procedural pulmonary complications. Conversely, thanks to the possibility of clearing the airways under NIV, FBO may improve gas exchange and, potentially, reduce the need for endotracheal intubation [87].

The literature [63, 96–113] reports different acute scenarios of synergistic interaction between FBO and NIV (figure 3).

The majority of the published studies used NIV (with the inclusion of CPAP) to prevent respiratory deterioration in spontaneously breathing ARF patients undergoing diagnostic FBO (table 3) [63, 96–113]. Most of them were uncontrolled heterogeneous studies in terms of severity and type of ARF, underlying diseases, setting of treatment, modes of ventilation, NIV interface, method of performing FBO during NIV and FBO procedures. Rates of success in avoiding intubation varied from 89% to 100%. Two RCTs compared the efficacy and safety of NIV *versus* oxygen in "assisting" nonventilated patients receiving FBO. In the first RCT conducted on 30 patients (P_{aO_2} $\leqslant$125 mmHg under an oxygen

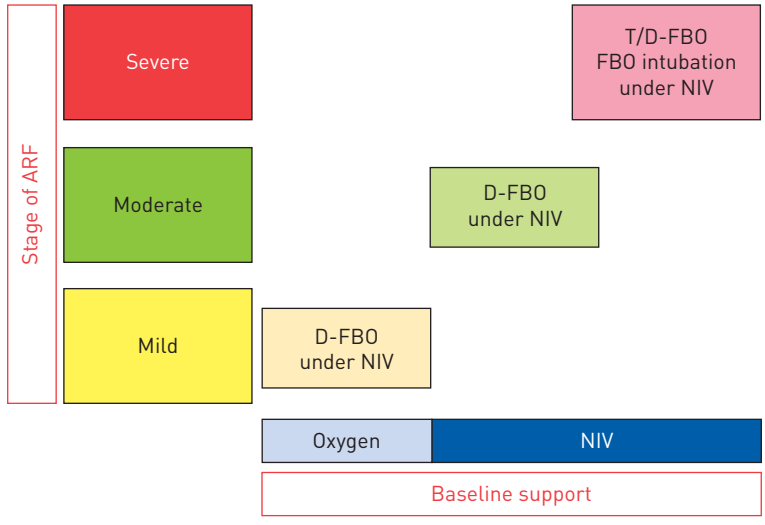

Figure 3. Different acute scenarios of a synergistic interaction between flexible bronchoscopy (FBO) and NIV. Mild: pH >7.35 and/or P_{aO_2}/F_{IO_2} 200–300 mmHg; moderate: pH 7.25–7.35 and/or P_{aO_2}/F_{IO_2} 100–200 mmHg; severe: pH <7.25 and P_{aO_2}/F_{IO_2} <100 mmHg. ARF: acute respiratory failure; D: diagnostic; T: therapeutic. Modified from [87].

mask) with suspected pneumonia, MAITRE *et al.* [98] showed significantly higher S_{pO_2} values during and 30 min after FBO with CPAP compared with oxygen therapy. Not only did the patients in the oxygen group develop hypoxaemia during FBO, but five patients in the oxygen group (compared with none in the CPAP group) also required ventilatory assistance within 6 h following the procedure. In another RCT involving 26 patients with HAP (P_{aO_2}/F_{IO_2} ⩽200 mmHg), ANTONELLI *et al.* [99] reported that compared with the oxygen group, the NIV group showed higher P_{aO_2}/F_{IO_2} values during and 60 min after FBO, as well as lower heart rate and mean arterial pressure values after FBO. One patient in the NIV group and two patients in the oxygen group required nonemergency intubation. Accordingly, prophylactic NIV is able to ensure adequate gas exchange during FBO in spontaneously breathing hypoxaemic patients, thus preventing intubation [1, 87].

Two uncontrolled studies [103, 104] investigated the feasibility, effectiveness and safety of FBO with BAL in hypoxaemic patients (P_{aO_2}/F_{IO_2} <200 mmHg) requiring NIV before the procedure. The rate of intubation at 48 h after FBO was much higher (39–45%) than that reported in studies dealing with prophylactic NIV during FBO (0–11%). According to the limited data, patients requiring NIV prior to FBO are at high risk of intubation and therefore FBO should be considered only in selected cases if intubation is available promptly [1, 87].

One case–control study [105] reported the effectiveness of early therapeutic FBO to avoid NIV failure for excessive secretions as compared with FBO after IMV in 30 acidotic COPD patients with hypercapnic encephalopathy. 2 h of NIV plus FBO significantly improved gas exchange, "sensorium" and cough efficiency without major complications. Improvement in acidosis, as well as hospital mortality, and durations of hospitalisation and ventilation were similar in the NIV-FBO *versus* IMV-FBO group. The NIV-FBO strategy significantly reduced infectious complications and requirement for tracheostomy. Even if this strategy may be a successful alternative to IMV in selected COPD patients, larger RCTs are necessary to confirm this result.

Table 3. Studies evaluating the combined use of flexible bronchoscopy (FBO) and NIV in different acute respiratory failure (ARF) scenarios

First author [ref.]	Year	Study	Patients n	Type of ARF and population	Support pre-FBO	Indication for FBO	FBO procedures	ETI at 48 h %
Antonelli [96]	1996	Prospective, observational	NIV: 8	Hypoxaemic, suspected pneumonia	Oxygen	Diagnostic	BAL	NIV: 0
Da Conceicao [97]	2000	Prospective, observational	NIV: 10	Hypoxaemic–hypercapnic, COPD	Oxygen	Diagnostic	BAL	NIV: 0
Maitre [98]	2000	RCT	Oxygen: 15; CPAP: 15	Hypoxaemic, suspected pneumonia	Oxygen	Diagnostic	BAL, BB	Oxygen: 46.7; CPAP: 6.7
Antonelli [99]	2002	RCT	Oxygen: 13; NIV: 13	Hypoxaemic, suspected pneumonia	Oxygen	Diagnostic	BAL	Oxygen: 15.4; NIV: 7.7
Bourgain [106]	2007	RCT	Oxygen: 16; NIV: 16	Ear, nose and throat surgery	None	Difficult ETI	FBO-assisted ETI	NA
Chiner [101]	2010	Prospective, observational	NIV: 35	Hypoxaemic, miscellaneous	Oxygen	Diagnostic	BW, PSB, BAL, BB	NIV: 0
Heunks [102]	2010	Prospective, observational	NIV: 12	Hypoxaemic, miscellaneous	Oxygen	Diagnostic	BAL	NIV: 8.3
Scala [105]	2010	Prospective, case–control	NIV: 15; IMV: 15	Hypoxaemic–hypercapnic, COPD	NIV	Diagnostic/ therapeutic	BAL	NIV: 20
Baumann [103]	2011	Prospective, observational	NIV: 40	Hypoxaemic, miscellaneous	NIV	Diagnostic	BAL	NIV: 10
Clouzeau [113]	2011	Prospective, observational	NIV: 23	Hypoxaemic, miscellaneous	NIV	Diagnostic	BAL	NIV: 17.4
Agarwall [63]	2012	Prospective, observational	NIV: 6	Hypoxaemic, acute ILDs	Oxygen	Diagnostic	BAL, TBLB	NIV: 1.7
Cracco [94]	2013	Prospective, observational	Oxygen and NIV: 169	Hypoxaemic, miscellaneous	Oxygen and NIV	Diagnostic	BAL	Oxygen and NIV: 15
Barjaktarevic [108]	2015	Prospective, observational	NIV: 10	Hypoxaemic, NA	NIV	ETI in NIV failure	FBO-assisted ETI	NA
Korkmaz Ekren [104]	2016	Prospective, observational	NIV: 28	Hypoxaemic, miscellaneous	NIV	Diagnostic	BAL	NIV: 39.3

ETI: endotracheal intubation; BB: bronchial biopsy; BW: bronchial washing; PSB: protected specimen brushing; IMV: invasive mechanical ventilation; ILD: interstitial lung disease; TBLB: transbronchial lung biopsy; NA: not available.

The combined use of FBO and NIV may be useful to perform intubation in two contexts: difficult airways and NIV failure. First, according to a RCT performed on 32 patients with anticipated difficult intubation in ear, nose and throat surgery [106], NIV was more effective than spontaneous breathing to improve ventilation during FOI performed under propofol. This issue may be particularly critical in obstructive sleep apnoea syndrome because of the risk of severe hypoxaemia due to upper airway collapse under sedation; working as "functional airways stenting", NIV/CPAP may facilitate FOI [109]. Second, intubation is challenging in severely hypoxaemic patients who deteriorate under NIV due to risk of major cardiovascular complications when the mask is removed [110]. Two small pilot studies [107, 108] reported the feasibility and safety of FOI under sedation during NIV in patients with either hypercapnic and/or hypoxaemic ARF who had developed NIV failure. These preliminary findings require confirmation by large RCTs comparing conventional *versus* FBO-guided intubation under NIV in patients with either predicted or proven difficult direct laryngoscopy, or with NIV failure due severe hypoxaemia.

Synergistic use of rigid bronchoscopy and NIV has been reported in two RCTs [111, 112] showing that as compared with both assisted spontaneous breathing and external high-frequency oscillation, NIV delivered by a poncho-wrap to support rigid bronchoscopy procedures under general anaesthesia was associated with lower incidence and severity of acidosis, lower requirement for increased oxygen supply, lower use of opioids, shorter recovery time, and reduced need for assisted manual ventilation. The applicability of this technique is limited as these favourable results were obtained by only one expert centre.

Practical issues

NIV-assisted FBO may be performed not only in the ICU/RHDCU, but also in other settings (*i.e.* the bronchoscopy unit) by physicians with expertise in both NIV and FBO who could also deal with cardiopulmonary complications and airways management [28, 87]. In nonventilated patients, NIV should be initiated at least 15–20 min before FBO and kept for 30–90 min after the procedure. The easiest mode of "assisting" FBO in hypoxaemic patients consists of delivering CPAP by means of a Boussignac system with an orofacial mask because this device remains open to the atmosphere [98]. When FBO is performed under NIV, initial low levels of pressure support (*i.e.* 10 cmH_2O) and PEEP (*i.e.* 5 cmH_2O) are suggested. With ICU ventilators (*i.e.* a double-tube circuit, ventilatory monitoring and F_{IO_2} setting), pressure support could be titrated in order to achieve an expiratory tidal volume of 8–10 $mL \cdot kg^{-1}$ and respiratory rate <25 $breaths \cdot min^{-1}$. In the case of hypoventilation, air leaks should be minimised; then, if the mask fitting is fine, pressure support could be increased. F_{IO_2} is set to achieve S_{pO_2} >90%. Patients who remain hypoxaemic despite high F_{IO_2} and PEEP levels are not good candidates for NIV-assisted FBO. Although many interfaces have been applied for NIV-FBO procedures, the most widely used is the orofacial mask (figure 4). The bronchoscope could be introduced through the nasal or oral route depending on the mask used and the operator's experience [28, 87]. The oral route requires direct introduction of the bronchoscope through a sealed connector inserted between the mask and the circuit; a mouthpiece is recommended to prevent damage to the instrument. Conversely, nasal access is challenging as the bronchoscope has to be considerably manipulated with risks of injuring both the nasal mucosa and instrument. In additional to topical anaesthesia, analgo-sedation may be considered for facilitating NIV-assisted FBO [113]. Risks of the NIV-FBO approach are related to both NIV (*e.g.* gastro-distension, pulmonary aspiration, hypoventilation and skin

Figure 4. Flexible bronchoscopy under NIV assistance *via* a face mask.

breakdown) and FBO procedures (*e.g.* cardiovascular events, hypoxaemia, bleeding and pneumothorax), as well to analgo-sedation [28, 87, 114].

Bronchoscopy during HFNC oxygen therapy

HFNC oxygen has been increasingly applied to different patterns of hypoxaemic ARF, due to its advantages over conventional oxygen therapy (*e.g.* delivery of high FIO_2, adequate humidification, patient comfort and provision of low PEEP values) [115]. Few studies have assessed HFNC oxygen during FBO [29, 115–117]. In a RCT comparing HFNC oxygen *versus* conventional oxygen therapy in 45 mildly hypoxaemic patients undergoing FBO [116], oxygenation was significantly better at the end of the procedure with HFNC oxygen at a higher flow rate (60 $L \cdot min^{-1}$) compared with HFNC oxygen at a lower flow rate (40 $L \cdot min^{-1}$) or oxygen through a Venturi mask. In another RCT [117], NIV was superior to HFNC oxygen with regard to oxygenation before, during and after FBO performed in 40 patients with moderate-to-severe hypoxaemia; no differences in intubation rate were observed at 24 h after the FBO between patients treated with NIV and HFNC oxygen. Further evidence is required to define the role of HFNC oxygen to support nonventilated patients during FBO.

Bronchoscopy during IMV

Cardiopulmonary changes induced by FBO are similar in spontaneously breathing and invasively ventilated patients. During IMV, the degree of these effects is dependent on the gap between the external diameter of the bronchoscope and the internal diameter of the ETT/tracheostomy tube. Bronchoscopes in nonintubated patients occupy 10–20% of the cross-sectional area of the trachea. In contrast, a 5.7-mm bronchoscope occupies 40% of a 9-mm ETT and 66% of a 7-mm ETT. Failure to recognise this matching may lead to inadequate ventilation with "air trapping" and damage to the bronchoscope [1]. The LMA

accommodates a larger bronchoscope, generating lower flow resistance values than the corresponding sizes of ETTs [118]. The external diameter of a bronchoscope should be carefully selected according to the size and type of the airway device used during IMV (ETT, tracheostomy tube or LMA) [1].

In IMV patients, pre-oxygenation with a F_{IO_2} of 1.0 is recommended during and immediately after FBO. The ventilator should be adjusted to a mandatory setting, avoiding triggered modes that are not reliable in maintaining ventilation during FBO. The ventilator pressure limit should be increased to ensure that adequate tidal volumes are delivered during each respiratory cycle and the ventilator rate increased if necessary. A special swivel connector with a perforated diaphragm, through which the bronchoscope can be inserted, allows maintenance of PEEP/CPAP, which is crucial in severe ARDS patients [1]. Small studies [119–121] have supported the use of jet and high-frequency positive-pressure ventilation during FBO in intubated patients, but more RCTs are needed to confirm any potential benefit of these techniques.

FBO should be undertaken cautiously in ventilated patients with head injury, as intracranial pressure may increase significantly due to carbon dioxide retention [122, 123]. A small RCT [124] showed that hyperventilation is useful in reducing the rise in intracranial pressure during FBO in IMV patients with closed head injury.

Conclusions

Bronchoscopy plays a fundamental role for the management of acute patients, both in the bronchoscopy room and in the ICU/RHDCU. Knowledge of the pitfalls and indications of bronchoscopy in ventilated and nonventilated patients is necessary to obtain the benefits and avoid the potentially life-threatening complications. The setting where acute bronchoscopy is performed should be able to adequately monitor patients, and to manage airway difficulties and cardiopulmonary emergencies. Acute bronchoscopy is useful to facilitate/guide procedures for airway management (*e.g.* FOI and PDT), support diagnosis of lung infiltrates in nonventilated and ventilated patients (*e.g.* VAP and ILD), and manage severe CAO and massive haemoptysis. Although the evidence that exists in favour of the combined use of NIV and bronchoscopy in different scenarios is variable, the best evidence supports prophylactic NIV to prevent intubation during FBO in nonventilated hypoxaemic patients. The role of HFNC oxygen in "assisting" FBO needs to be further investigated.

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Chest tube insertion

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Chest tube placement into the pleural cavity is performed to drain abnormal collections of air or fluid, or as a means to instil medications to perform pleurodesis. The choice of chest tube and insertion site depends on the indication for placement and the nature of the fluid/air to be drained. Small drains should be used for pneumothorax, free-flowing pleural effusions and pleural infection, and analgesia should be considered as a pre-medication. It is strongly recommended that all chest tubes for fluid should be inserted under image guidance. The tube should be inserted using full aseptic technique, and substantial force should never be used. Blunt dissection should be employed in cases of trauma or insertion of large-bore drains. Chest tubes should be managed on wards familiar with their management, and checked daily for fluid drainage volumes and any signs of wound infection, and documented for swinging and/or bubbling. The chest tube should be removed once pneumothorax has resolved and fluid drainage has decreased to <200 mL per day.

Chest tube insertion is a procedure in which a tube is placed through the chest wall into the pleural cavity, primarily to drain an air, fluid or blood collection from the pleural space.

Hippocrates' writings described how open drainage of the thorax was frequently performed in the fifth century BC [1]. The first clear evidence of a chest tube procedure can be found in Wolfram von Eschenbach's *Parzival*, written between 1210 and 1220 [2]. In 1873, Playfair first described the closed drainage of the pleura in a 7-year-old child suffering from thoracic empyema [3]. Following the First World War, rib resection and open drainage was attempted, but it was not until the late 1950s that tube drainage became widely used [4, 5].

Insertion of a chest tube is a relatively simple procedure but with the potential to cause significant morbidity and mortality if performed by inexperienced doctors [6]. Elective chest tube insertion should be avoided out of normal hours, except in the case of significant respiratory or cardiovascular compromise, because the rate of complications is higher [7].

Here, we will review the indications and contraindications and use of imaging for chest tube insertion, and the techniques, management and complications of chest tubes.

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Indications and contraindications

Chest tube placement is indicated for the conditions shown in table 1.

Contraindications are relative and depend greatly on the urgency with which the tube needs to be placed. Use of anticoagulants, and known bleeding disorders or abnormal coagulation, are all relative contraindications. Ideally, anticoagulation will be reversed or withheld while the procedure is performed. Non-urgent chest drain insertions should be avoided in anticoagulated patients until the international normalised ratio (INR) is <1.5 [7]. In more urgent cases, attempts to correct severe coagulation defects should be undertaken in consultation with a haematologist.

Long-acting antiplatelet agents may be safe to continue when placing a small-bore tube, but there is no good RCT evidence [8, 9].

Use of imaging

Chest radiography

The plain chest radiograph features of pleural effusion or pneumothorax are usually characteristic. In the case of pneumothorax, the chest radiograph demonstrates a visible visceral pleural edge seen as a very thin, sharp, white line. No lung markings are visible peripherally to this line, and the peripheral space is radiolucent compared with the adjacent lung. In a pleural effusion, the posteroanterior chest radiograph will show at least blunting of the costophrenic angle, and potentially no lung markings may be visible. There is often dense opacification of the hemithorax, without air bronchograms. Sometimes, there is a mediastinal shift away from the side of the effusion.

Table 1. Indications for chest tube insertion

Pneumothorax
Large primary spontaneous pneumothorax persisting after needle aspiration
Secondary spontaneous pneumothorax
Traumatic pneumothorax: large symptomatic iatrogenic pneumothorax, most commonly due to lung biopsy or central line placement/pacemaker insertion
All patients on mechanical ventilation
Tension pneumothorax
Post-operative bronchopleural fistula/post-thoracoscopy
Pleurodesis for treatment of secondary pneumothorax in patients unfit for operative intervention
Pleural effusion
Infected effusion (*i.e.* parapneumonic effusion, empyema)
Symptomatic malignant effusion
Chylothorax
Other effusions: symptomatic effusions of other aetiology (*e.g.* cardiac failure, renal failure, hepatic effusion), considering and balancing benefits *versus* risks
Pleurodesis for the treatment of refractory effusion (predominantly malignancy)
Post-operative following thoracic or upper abdominal surgery
Haemothorax
Chest trauma (blunt or penetrating)
Post-operative following thoracic or upper abdominal surgery

Ultrasound

Thoracic ultrasound guidance is strongly recommended for all pleural procedures for pleural fluid [7]. Ultrasound guidance not only improves the rate of successful chest tube insertion but also reduces the risks associated with the procedure [10].

CT

CT is helpful in tube placement in complex pneumothorax/loculated fluid/adhesions and to distinguish a bulla from a pneumothorax. It is also helpful in diagnosing occult pneumothorax in mechanically ventilated patients. Sometimes, tubes may need to be placed under direct guidance.

Pre-procedure preparation

Training

All doctors who perform chest tube insertion should be appropriately trained and should have been supervised initially by an experienced trainer. A survey of UK National Health Service Trusts showed that the majority did not have a formal training policy for chest drain insertion in 2008 [4].

Consent

Written information should be provided before the consent process, except in emergency situations. Written informed consent should be taken where the patient is competent and should be obtained by a member of staff trained in the procedure or adequately trained to take consent.

Clotting disorders and anticoagulation

Non-urgent chest drain insertions should be avoided in anticoagulated patients until the INR is <1.5 [5].

Antibiotic prophylaxis

Antibiotic prophylaxis is not indicated for nontrauma patients requiring a chest drain [11]. Antibiotic prophylaxis should be considered for trauma patients requiring chest drains, especially after penetrating trauma [12].

Equipment

The equipment used for chest tube insertion is listed in table 2. Equipment for the Seldinger technique is also available in a packed kit form (figure 1).

Table 2. Equipment used for chest tube insertion

Ultrasound machine for effusions
Sterile gloves and gown
Skin antiseptic solution (*i.e.* iodine or chlorhexidine in alcohol)
Sterile drapes
Local anaesthetic (*e.g.* lidocaine 1%)
A selection of syringes (10–20 mL) and needles (21–25 G)
Scalpel and blade
Suture (*e.g.* 0 or 1–0 silk)
Instrument for blunt dissection if required (*e.g.* artery forceps)
Guide wire and dilators for Seldinger technique
Chest tube
Connecting tubing
Closed drainage system (including sterile water if an underwater seal is being used)
Gauze swabs and dressings

Tube selection

There is no consensus regarding the size of chest tube that should be inserted for pneumothorax, pleural effusion, empyema or haemothorax (figure 2).

Overall, small tubes should be used as the first-line therapy for pneumothorax, free-flowing pleural effusions and pleural infection [7]. Small-bore tubes have significantly lower pain scores and analgesia requirements and a greater degree of comfort than in comparable patients in whom large-bore catheters have been inserted for the same indication [13–16]. Recent randomised trial data showed placement of 12-French chest tubes was associated with a statistically significant but clinically modest reduction in pain when compared with 24-French chest tubes [16].

Figure 1. Prepacked 12-French Seldinger chest tube kit (Rocket Medical, Washington, UK).

Figure 2. Argyle chest tubes of different sizes (Covidien, Tullamore, Ireland).

In trauma, Inaba *et al.* [17] performed a prospective analysis of 28–32-French *versus* 36–40-French chest tube sizes and showed that chest tube size did not have an impact upon the clinically relevant outcomes. Specifically, there was no difference in the efficacy of drainage, rate of complications including retained haemothorax, need for additional tube drainage or invasive procedures. Furthermore, tube size did not affect the pain felt by patients at the site of insertion in this particular study; however, these would all be considered large drains [17].

For patients at risk of a large air leak due to bronchopleural fistulae (*e.g.* on mechanical ventilation, bronchial dehiscence), a larger-bore tube is generally believed to be superior (*e.g.* 24-French), although scientific evidence is lacking [18, 19].

If a small-bore tube fails, large-bore tubes may be successful, although other studies suggest image-guided small-bore catheters can be therapeutically successful when large-bore tubes fail [20, 21].

Analgesia and sedation

Chest tube insertion can be associated with pain and anxiety [22]. To reduce the pain associated with chest drains, analgesia should be considered as pre-medication. Analgesia should be prescribed for all patients with a chest drain in place. The patient needs to be reassured before and during the procedure to reduce the anxiety associated with the procedure. Good local anaesthesia is key in reducing pain.

In addition to local analgesia with lidocaine, in a haemodynamically stable patient, conscious sedation with an opioid or a benzodiazepine (as per local policy) may be considered. Patients given conscious sedation must be appropriately monitored from a cardiorespiratory perspective.

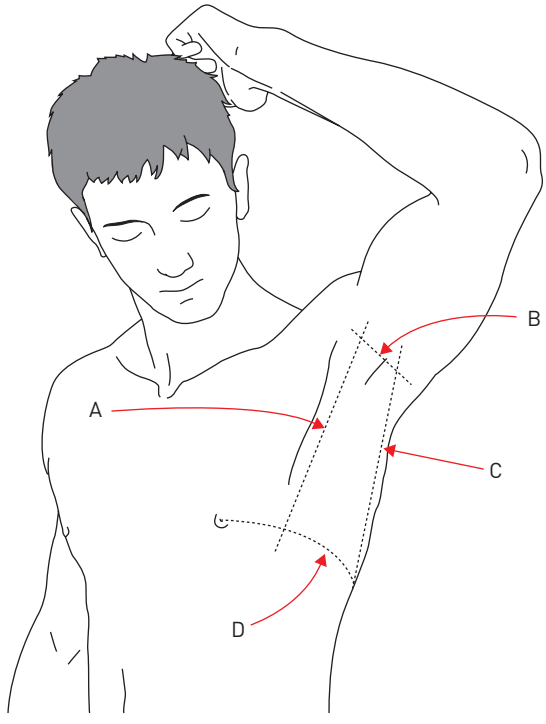

Figure 3. The "triangle of safety". A: lateral edge of pectoris major; B: base of axilla; C: lateral edge of latissimus dorsi; D: fifth intercostal space.

Insertion site

Ideally, insertion should be in the "triangle of safety", an area bordered by the lateral edge of the latissimus dorsi, the lateral border of the pectoralis major muscle and a line superior to the horizontal level of the nipple (figure 3) [7]. If the chest tube is to be inserted into a loculated pleural effusion, the site of insertion should be guided by imaging. For apical pneumothoraces, the second intercostal space in the mid-clavicular line may be more appropriate but is not recommended routinely. It may be the preferred site when using a small drain with an ambulatory drainage system.

Ideally, patients should be in the lateral decubitus position, slightly rotated, and with the arm on the side of the lesion placed behind the patient's head. Sometimes patients are more comfortable in a semi-recumbent position. An alternative is for the patient to sit upright leaning over an adjacent table with a pillow under the arms if the drain needs to be inserted posteriorly (under ultrasound guidance).

Techniques

Local anaesthesia is first performed, as described in table 3. Once the site is prepared and anaesthetised, one of two techniques is then commonly used to place a chest tube. The standard technique employs blunt dissection to access the pleural space (table 4). In contrast, the Seldinger technique uses serial dilation over a guidewire (table 5) and has become the most widespread method of tube insertion. The Seldinger technique is useful

Table 3. Procedure for local anaesthesia

Step	Procedure
1	Chest tube insertion should take place in a clean area using full aseptic technique including gowns, drapes, sterile gloves and skin cleansing.
2	Place the patient in the preferred position as described in the main text.
3	Perform a pleural ultrasound prior to chest tube insertion and mark the site of insertion.
4	Perform a surgical hand wash, and put on a surgical gown, mask and sterile gloves.
5	Open the chest drain pack.
6	Clean the skin using an antiseptic skin preparation, such as chlorhexidine, and swab in a circular motion from the point of insertion outwards in a circular motion.
7	Place sterile drapes to maintain the sterile field.
8	Insert local anaesthetic initially, with an orange needle (25 G); this will make a bleb of anaesthetic just below the skin surface. Change to a green needle (21 G) and anaesthetise the intercostal muscles, other soft tissues and pleura. Once free air or fluid is aspirated, withdraw the needle a few millimetres until aspiration ceases. Then inject 1–2 mL of local anaesthetic.
9	Aspirate as the needle is inserted to prevent injection into a vessel and to help locate fluid or air in the pleural cavity.

Table 4. Procedure for blunt dissection following local anaesthesia

Step	Procedure
1	Once free air or fluid has been aspirated, make an appropriate incision in the skin with the incision length just greater than the diameter of the tube at the site of the lidocaine injection parallel to the intercostal space.
2	Perform blunt dissection using artery forceps through the subcutaneous tissues (open and close forceps to separate rather than cut tissues). This is to avoid injury to the neurovascular bundle that runs along the inferior aspect of the rib.
3	After a few passes, you should feel a sudden give and sometimes a hiss of air or flow of fluid.
4	Insert a finger through the tract into the pleural space to confirm proper position and make sure there are no adhesions between the lung and the pleural surface.
5	Insert the tube through the tract and advance the chest tube until the last drainage hole is within the thoracic cavity by at least 2 cm.
6	Aim the drain towards the apex in the case of pneumothorax, or inferiorly and posteriorly for effusion.
7	Confirm that the chest tube is in the thoracic cavity by observing condensation within the tube with respiration, or drainage from the tube.
8	Place a suture to anchor the chest tube. Attach the end of the tube onto the underwater drainage system. Check that the water in the chest drain is bubbling or fluctuating ("swinging"); if in doubt, ask the patient to cough gently.
9	Remove the drapes. Secure the drain to the skin using some cut swabs and a dry adhesive dressing.
10	Dispose of all waste and sharps appropriately.
11	Obtain a chest radiograph to confirm position of the chest tube, and document the findings in the clinical notes.
12	Start a chart for recording chest tube activity (swinging, bubbling and drainage).
13	After the procedure, inform the patient regarding chest tube advice. They should be advised to make sure that the chest drainage system is kept below the level of the chest at all times.

Table 5. Procedure for the Seldinger technique following local anaesthesia

Step	Procedure
1	Insert an introducer needle into the pleural space and confirm that either fluid or air is returned. If this does not occur, do not proceed.
2	If fluid or air is returned, the syringe is removed.
3	Insert the guidewire through the introducer needle into the pleural space. The wire should pass without resistance. If this is not the case, the needle can be repositioned if this is practical. Otherwise, the procedure should be abandoned.
4	The introducer needle is then removed, leaving the guidewire in position.
5	Pass the dilators sequentially over the guidewire to dilate the tract in a slight twisting action. Never use force.
6	Remove the dilator (or serial dilators).
7	Pass the chest tube into the pleural space over the guide wire.
8	Remove the guidewire and any tube stiffeners, leaving the chest tube in place.
9	Secure the tube in place with a suture, dress with gauze, connect the drainage system, obtain a chest radiograph to confirm the tube position and assess lung expansion, and monitor the initial drainage from the tube as described in the main text.

for the placement of smaller-bore tubes that drain air and nonviscous fluids, and must be performed with the aid of ultrasound for fluids.

Management

Drainage

Drainage must be monitored. Some examples of drainage systems are given in table 6.

Level of suction

In medical situations, there is no evidence to recommend or discourage the use of suction. However, suction is common practice, especially in the treatment of nonresolving

Table 6. Drainage systems

System	Description
Underwater seal bottle	Tube is placed under water at a depth of ~3 cm with a side vent, which allows the escape of air or which may be connected to a suction pump
Heimlich valve [23, 24]	Ambulatory drainage system
Flutter bag	Ambulatory drainage system
Digital chest drainage system[#] [25, 26]	Provides regulated negative pressure close to the patient's chest Shows actual air leak data Patients enjoy freedom of mobility without being attached to wall suction Timely decision regarding chest drainage management

[#]: Thopaz Digital Chest Drainage System; Medela Inc. Healthcare, McHenry, IL, USA.

pneumothorax. A persistent air leak, without incomplete re-expansion of the pneumothorax on a chest radiograph, is the usual reason for applying (or increasing) suction [27]. If suction is required, this may be done by the underwater seal at a level of 10–20 cmH_2O. Higher levels of suction may be associated with significant discomfort.

Removal of the chest tube

The presence of an air leak or fluid drainage should be assessed daily to determine whether the tube can be removed. To reduce the risk of infection complications, the tube should be removed as soon as it is safe to do so.

For pneumothorax, when the lung is fully expanded and there is no visible air leak without suction, the chest tube can be removed. As a general rule, the chest tube should not be clamped. This is the safe approach in most instances to avoid clamping being carried out inappropriately by less experienced clinicians.

For pleural effusion, once the daily output of drainage fluid is <200 mL per day and the lung is fully expanded, the chest tube may be removed. However, there is little evidence as to the minimum fluid volume associated with successful removal [28, 29].

Removal technique

If the above removal criteria are met, the suction is eliminated (if applied). While some advocate pulling the chest tube at end-inspiration, others advocate end-expiration. A small study comparing these two techniques did not show a difference in post-pull pneumothorax [30]. The procedure should be explained to the patient. The patient should rehearse this several times prior to the actual tube removal. Remove the chest tube quickly while placing a dry sterile dressing over the opening. Once the tube has been removed, secure the dressing with tape.

There is no evidence that a chest radiograph should be performed routinely in medical patients, although this is common practice in some areas. Case series in cardiac surgery patients suggest that it is not required [31–33].

Complications

Complications from chest tube placement are related to the indication for insertion, circumstances (*i.e.* elective *versus* emergency), experience and training of the clinician [34].

Complications of chest tube placement include malposition, infection (*e.g.* empyema), organ injury (*e.g.* lung, diaphragm, heart, liver or spleen) and pulmonary oedema related to rapid pulmonary expansion (reducing the volume drained to 1.5 L at a time appears to mitigate this) [27, 28, 35, 36].

The incidence of these complications ranges from 1% to 6% and is related to the diameter of the tube, with small-bore tubes having fewer complications [37].

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